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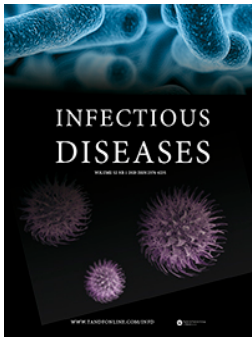
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External validation of the HANDOC score – high sensitivity to identify patients with non-beta-haemolytic streptococcal endocarditis

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ABSTRACT

Background: Invasive infections with non-beta-haemolytic streptococci (NBHS) is quite common and presents the clinicians with difficulties regarding which patients are at risk for infective endocarditis (IE). The HANDOC score was developed to identify patients with NBHS bacteraemia who are at low risk of IE. This study was conducted to validate HANDOC in an external cohort.

Methods: Patients with NBHS in blood cultures between March and September 2016 in a Danish centre were included as part of an on-going study. Patient characteristics were collected to classify bacteria according to Dukés criteria and the components of the HANDOC score were collected retrospectively from the patients' medical records.

Results: 68 patients were included in the cohort, of which 16 fulfilled Dukés criteria for IE. All patients with IE (16 of 16) had a HANDOC score above the predefined cut-off. Cases of IE were found in patients with *Streptococcus mitis*, *Streptococcus bovis*, *Streptococcus mutans*, *Streptococcus anginosus*, and *Streptococcus sanguinis* group streptococci. The HANDOC score thus had a sensitivity of 100% and a specificity of 62% in this cohort.

Conclusions: HANDOC has a sensitivity of 100% and a relatively high specificity (62%) also in a prospectively enrolled cohort of patients from another country than its origin. This indicates that HANDOC can be implemented in clinical practice to identify patients with a low risk of IE in whom echocardiography can be omitted.

KEYWORDS

Endocarditis
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echocardiography
streptococcus
management score

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Table 1. Components of the HANDOC-score [6].

| Variable | Components of score | Points given or subtracted |
|--|----------------------------|----------------------------|
| Heart murmur or valvular disease | | 1 |
| Aetiology | <i>S. bovis</i> group | 1 |
| | <i>S. mutans</i> group | 1 |
| | <i>S. sanguinis</i> group | 1 |
| | <i>S. anginosus</i> group | -1 |
| | <i>S. mitis</i> group | 0 |
| | <i>S. salivarius</i> group | 0 |
| Number of positive blood cultures ≥ 2 | | 1 |
| Duration of symptoms ≥ 7 days | | 1 |
| Only one species in blood cultures | | 1 |
| Community acquired infection | | 1 |

Introduction

Bloodstream infection with non-beta-haemolytic streptococci (NBHS) is not unusual [1]. Infective endocarditis (IE) is a serious infection and NBHS are among the most commonly isolated pathogens [2–5]. IE is, however, only diagnosed in a small proportion of patients with NBHS bacteraemia [6]. The diagnosis of IE is mainly based on microbiological findings in blood combined with findings on transesophageal echocardiography (TEE) [7,8]. Since TEE is not available at all hospitals, not available at all hours of the day and is uncomfortable for the patient, it seems reasonable to perform this investigation on patients with NBHS bacteraemia at substantial risk for IE. To guide clinicians when to pursue IE investigations in NBHS bacteraemia, the HANDOC score was developed and published in 2017 [6]. HANDOC is a score system developed to estimate the risk of IE in patients with bacteraemia caused by NBHS. With a cut-off between 2 and 3 points, one point is given for the presence of heart murmur or heart valve disease (H). One point is added if the aetiological organism is in the *S. bovis*, *S. mutans* or *S. sanguinis* groups, and subtracted if it is in the *S. anginosus* group (A). One point is also added if the number of positive cultures is two or more (N), one if the duration of symptoms is one week or more (D), one if there is only one species in the blood cultures (O), and one point if the infection is community-acquired (C) [6]. In the original study, the score was validated using a separate control cohort from the same geographical area. The present study was conceived to evaluate the HANDOC score using a prospectively enrolled cohort of patients with NBHS at a different geographical location.

Methods

Patients were included prospectively as part of an ongoing study on the use of echocardiography in bacteraemia with Gram-positive bacteria. Inclusion was

based upon having a positive blood culture that was analyzed at North Zealand Hospital and Herlev-Gentofte Hospital (both located in Denmark) between March and September 2016. According to local guidelines, transthoracic echocardiography (TTE) and TEE was recommended whenever a blood culture with growth of a Gram-positive bacterium typically found in IE (*Staphylococcus aureus*, NBHS, *Enterococcus faecalis* or coagulase-negative staphylococci (in ≥ 2 bottles)) was encountered. Data from the medical records was used to gain information about variables in the modified Duke criteria [7,8] and HANDOC scores [6,7] (permit from Data Protection Agency 2012-58-0004 (3-3013-1845/1)). Bacterial isolates were classified according to the original HANDOC study [6] (Table 1).

The patients were classified in the same way as in the original HANDOC study, and were considered to have IE if they fulfilled the modified Duke criteria for definite IE. If they did not fulfil the modified Duke criteria, they were classified as IE excluded or unknown. IE was excluded if either (1) a TEE was performed with no signs of IE or (2) the patient received an antibiotic treatment of less than 3 weeks in total with less than 14 days being intravenous and survived at least 6 months after inclusion in the study and without a relapse of bacteraemia. Statistical analysis was performed using SPSS 25 (IBM, Armonk, NY) and MedCalc (MedCalc software bvba). Chi-square and Student's *t* test for comparisons of proportions and means, respectively.

Results

The clinical and microbiological characteristics of the 68 included patients are shown in Table 2. IE was confirmed in 16 patients and in 52 patients IE was not present. Of 52 patients without IE, IE was excluded in 46 patients. Patients with IE were older (81 versus 76 years old) though the difference was not statistically significant. The gender distribution was similar in all groups with men constituting around 60% of patients.

Table 2. Clinical and microbiological characteristics in relation to IE.

| | All cases <i>n</i> = 68 | IE confirmed <i>n</i> = 16 | IE unknown <i>n</i> = 6 | IE excluded <i>n</i> = 46 | <i>p</i> value, IE confirmed versus excluded |
|---|----------------------------|-------------------------------|----------------------------|------------------------------|---|
| Age, median (range) | 72 (27–95) | 81 (42–89) | 69.5 (52–89) | 75.5 (27–68) | .23 |
| Gender, male | 41 (60) | 10 (63) | 3 (50) | 28 (61) | .91 |
| Heart valve disease or heart murmur, no | 21 (31) | 9 (56) | 0 (0) | 12 (26) | .029 |
| Heart valve disease, no | 16 (24) | 6 (38) | 0 (0) | 10 (22) | .22 |
| Heart murmur, no | 12 (18) | 7 (44) | | 5 (11) | .0045 |
| <i>S. mitis</i> group | 16 (24) | 2 (13) | 1 (17) | 13 (28) | .2 |
| <i>S. salivarius</i> group | 7 (10) | 0 (0) | 0 (0) | 7 (15) | .1 |
| <i>S. bovis</i> group | 15 (22) | 6 (38) | 1 (17) | 8 (17) | .1 |
| <i>S. mutans</i> group | 4 (5.9) | 2 (13) | 0 (0) | 2 (4.3) | .25 |
| <i>S. sanguinis</i> group | 8 (12) | 3 (19) | 0 (0) | 5 (11) | .42 |
| <i>S. anginosus</i> group | 18 (26) | 3 (19) | 4 (67) | 11 (24) | .68 |
| At least two positive blood cultures | 44 (65) | 16 (100) | 4 (67) | 24 (52) | <.001 |
| Symptom duration of >1 week | 17 (25) | 8 (50) | 2 (33) | 7 (15) | .0055 |
| Only one bacterial species | 55 (80) | 14 (88) | 4 (67) | 37 (80) | .53 |
| Community acquired, no | 33 (49) | 10 (63) | 1 (17) | 22 (48) | .31 |

TEE was performed on 55% of the patients. All but one of the patients with confirmed IE (94%) underwent TEE as compared to 50% of the patients where IE was excluded. All patients with IE underwent either TTE or TEE, compared to 64% of the patients without IE. Echocardiography was performed on 18 of the 33 patients with a HANDOC score below the cut off level of 3 points. The number needed to screen was 2.3 (95% CI 1.6–3.7) employing HANDOC. In the population studied the positive predictive value was 46% (95% CI 37–54) and the negative predictive value was 100%.

When the HANDOC score was used to distinguish patients with IE from other patients the sensitivity was 100% (95% CI 79.4–100) and the specificity was 62% (95% CI 47–75) (Figure 1). If patients from the unknown group were excluded from the analysis, the resulting sensitivity of HANDOC was still 100% whereas the specificity was 59% (95% CI 46–72).

Discussion

In this study on NBHS bacteraemia, the proportion of patients with IE was higher than in the recently published HANDOC study (24% compared to 8.5%). The rate of TEE was higher than in the original study (55% versus 12%, $p < .001$). HANDOC has excellent sensitivity to detect patients with IE in the present cohort but the specificity (58%) is lower than the one found in the original study (73%). This might be explained by a significantly higher proportion of cases having only one bacterial species reported in blood culture in this study than in the original study (80% versus 63%, $p = .007$), which in turn might be due to different microbiological demographics, to differences in when and how to take blood cultures, or to differences in how the microbiological laboratories identify and report findings. IE caused by *S. anginosus* group *Streptococcus* was not as

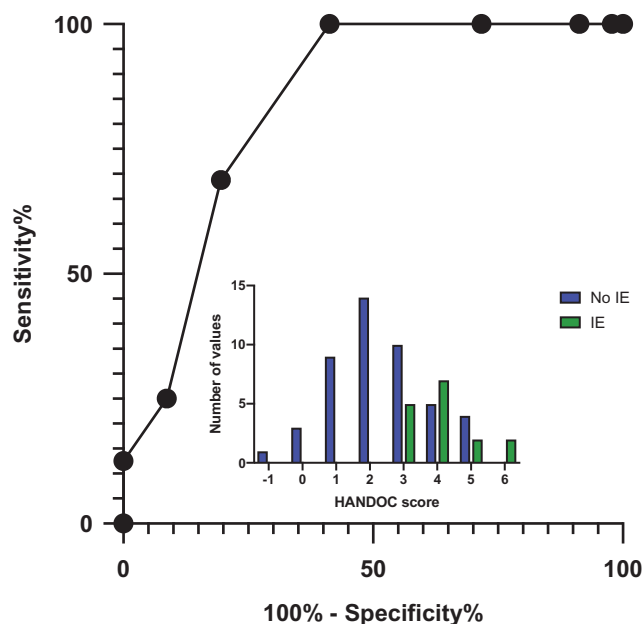


Figure 1. Receiver operating characteristic curve for the ability of HANDOC to separate patients with and without IE in this cohort. The inset shows the number of episodes of IE and non-IE in relation to the HANDOC score.

uncommon in this cohort as in the original study (19% versus 0%, $p < .001$), possibly due to different patient background or to different criteria for when to perform echocardiography. The patients with IE caused by *S. anginosus* were identified by the HANDOC score, however, and the design of this validation study is not appropriate for suggesting changes to the HANDOC score. The distribution of bacteria in the different streptococcal groups was similar to the distribution in the original study, though the proportion of *S. bovis* group isolates was somewhat larger. The clinical characteristics of the patients were also similar to those in the original study.

An obvious limitation of the present study is that the cohort is relatively small. We can thus not exclude that

HANDOC can miss cases of IE. A strength of the study is that the proportion of patients undergoing TEE was higher than in many previous studies on risk for IE in bacteraemia [6,9–11]. This makes it less likely that cases of IE were missed. In conclusion, the results show that HANDOC can be used to safely identify patients with NBHS where the risk of IE is so low that further IE investigations might be unnecessary. If other factors, not accounted for in the HANDOC score, lead the physician to suspect IE a low HANDOC score should of course not exclude the patient from TEE.

Disclosure statement

No potential conflict of interest was reported by the authors.

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