A multiple biomarker strategy for diagnosis and prognosis of acute heart failure in older patients presenting to the emergency department

Philipp Bahrman1, Anke Bahrman2, Benjamin Hofner2, Thomas Berndt3, Michael Christ5, Stephan Achenbach2, Cornel Sieber1

1 Institute for Biomedicine of Aging, Friedrich-Alexander-University, Nürnberg, Germany
2 Department of Cardiology, Friedrich-Alexander-University, Erlangen, Germany
3 Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander-University, Erlangen, Germany
4 Institute for Clinical Chemistry, Laboratory Medicine and Transfusion Medicine, Nürnberg Hospital, Germany
5 Department of Emergency and Critical Care Medicine, Nürnberg Hospital, Germany

**PURPOSE**

Biomarkers can help to identify acute heart failure (AHF) as the cause of symptoms in patients presenting to the emergency department (ED). Older patients may prove a diagnostic challenge due to co-morbidities. Therefore we prospectively investigated the diagnostic and prognostic performance of N-terminal pro-B-type natriuretic peptide (NT-proBNP) alone or in combination with other biomarkers for acute HF upon admission at the ED.

**METHODS**

We consecutively enrolled 302 non-surgical patients ≥70 years presenting to the ED. In addition to NT-proBNP, mid-regional pro-adrenomedullin (MR-proADM) and mid-regional pro-atrial natriuretic peptide (MR-proANP) or C-terminal pro-endothelin-1 (CT-proET-1) and ultra-sensitive C-terminal pro-vasopressin (Copeptin-us) were measured at admission. Two cardiologists independently adjudicated the final diagnosis of AHF after reviewing all available baseline data (excluding NT-proBNP, MR-proADM, MR-proANP, CT-proET-1 and Copeptin-us). All patients were followed up for cardiovascular-related death within the following 12 months.

**RESULTS**

AHF was diagnosed in 120 (40%) patients (age 81±6 years). Adding MR-ADM to NT-proBNP levels improved C-index (0.84 versus 0.81; P=0.045), and yielded IDI (3.3%; P=0.002), NRI (17%, P<0.001) and continuous NRI (33.3%; P=0.002). Adding CT-proET-1 to NT-proBNP levels improved C index (0.86 versus 0.81, P=0.031), and yielded robust IDI (12.4%; P<0.001). No other dual or triple biomarker combination showed a significant improvement of both C-index and IDI (fig. 1). Cox regression analysis revealed a 1.99-fold risk of death (95% CI 1.61 to 2.45, P<0.001) for an increment of the log-transformed MR-proADM concentration by 1 unit after adjustment for cardiovascular risk factors (fig. 2, table 1).

**CONCLUSIONS**

In older patients presenting to the ED, the addition of CT-proET-1 or MR-proADM to NT-proBNP improves diagnosis of HF. Both dual biomarker approaches offer significant risk reclassification improvement over NT-proBNP. MR-proADM improves the prognostic performance in AHF.

Table 1  Linear Cox Model

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Hazard Ratio</th>
<th>CI (lower)</th>
<th>CI (upper)</th>
<th>Standard Error</th>
<th>v value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.11</td>
<td>1.12</td>
<td>1.04</td>
<td>1.20</td>
<td>0.04</td>
<td>3.16</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex: male</td>
<td>-0.01</td>
<td>0.99</td>
<td>0.94</td>
<td>2.19</td>
<td>0.40</td>
<td>-0.2</td>
<td>0.985</td>
</tr>
<tr>
<td>MRproADM, nmol/L</td>
<td>0.69</td>
<td>1.99</td>
<td>1.61</td>
<td>2.45</td>
<td>0.11</td>
<td>6.46</td>
<td>0.001</td>
</tr>
<tr>
<td>hs-cTNT, ng/mL</td>
<td>-1.17</td>
<td>3.22</td>
<td>1.97</td>
<td>6.68</td>
<td>0.61</td>
<td>1.91</td>
<td>0.056</td>
</tr>
</tbody>
</table>

The authors declare no conflict of interest. P.B. and A.B. hold fellowships of the "Forschungkolleg Geriatrie" of the Robert Bosch Foundation.