Prior polyvascular disease: risk factor for adverse ischaemic outcomes in acute coronary syndromes

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Introduction

The presence of peripheral arterial disease (PAD) is a marker for atherosclerotic involvement of the coronary arteries.¹⁻¹⁰ Similarly, the presence of cerebrovascular disease (CVD) is associated with higher likelihood of coronary artery disease (CAD). In patients with stable atherosclerosis or with multiple risk factors for atherosclerosis, the presence of clinically evident involvement of two or
more arterial territories is detected in about one in six patients.\textsuperscript{11} Furthermore, patients with so-called ‘polyvascular’ disease have a markedly higher event rate over intermediate-term follow-up than do patients with atherosclerosis affecting only one arterial bed.\textsuperscript{12} Thus, polyvascular disease has been shown to be both common and hazardous in stable outpatients. Despite numerous advances, acute coronary syndromes (ACS) remain a major health care challenge.\textsuperscript{13–16} Several risk factors for worse in-hospital outcomes have been identified. However, the impact of polyvascular disease in patients with ACS has not been well characterized.

The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative is an ongoing dynamic registry that examines treatment patterns and in-hospital outcomes of patients presenting with ACS at many hospitals in the USA. The current analysis was performed to determine the prevalence of polyvascular disease in patients presenting with ACS and the impact on both ischaemic and bleeding outcomes.

**Methods**

**Definitions**

Peripheral arterial disease, a unique variable on the data collection form, was defined in the data definitions for CRUSADE as a history of any of the following conditions: claudication (either with exertion or at rest), amputation due to arterial insufficiency, vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities, documented aortic aneurysm, or a positive non-invasive test (e.g. ankle brachial index \( < 0.8 \)). Cerebrovascular disease was designated for patients with a history of prior stroke. Coronary artery disease was designated for patients with a history of prior myocardial infarction (MI), prior percutaneous coronary intervention (PCI), or prior coronary artery bypass grafting (CABG). Number of vascular territories with pre-existent atherosclerotic involvement was defined as the number of prior diseased territories among PAD, CVD, and CAD for each patient. Polyvascular disease was defined as pre-existing disease in multiple arterial territories (two or more vascular territories with pre-existent atherosclerotic involvement). The composite outcome of in-hospital ischaemic events was defined as any of the following: death, MI, stroke, or congestive heart failure (CHF).

**Study population**

Between 15 February 2003 and 30 September 2006, a total of 111,972 patients with non-ST-segment elevation (NSTE) ACS were enrolled into the CRUSADE registry at 486 sites in the USA. A total of 3340 patients were excluded from this analysis: 1917 had missing PAD information, 630 missing prior stroke, 255 missing prior MI, 246 missing prior PCI, and 202 missing prior CABG. Of these patients, 12,883 were transferred out of their initial hospital and were also excluded as data could not be collected after transfer due to current US privacy laws. This left a study population of 95,749 patients from 484 sites (Figure 1).

**Endpoint definitions**

In patients presenting without an MI, in-hospital MI was defined as CK-MB or troponin values above the upper limit of normal (ULN) or new, significant Q waves in at least two contiguous leads of an electrocardiogram (ECG). In patients presenting with an MI prior to revascularization, new, significant Q waves in at least two contiguous leads of an ECG or an increase in CK-MB or troponin above the ULN (if most recent cardiac markers prior to the event were normal) or an increase in CK-MB or troponin by \( \geq 50\% \) above the most recent value (if most recent cardiac markers prior to the event were above the ULN) was counted as an MI event. If the patient was within 24 h of PCI, an increase in CK-MB \( \geq 50\% \) above the level preceding the procedure (if the most recent cardiac markers prior to the procedure were above the ULN) or an increase in CK-MB to a value at least 3 \( \times \) the ULN (if the most recent cardiac markers prior to the procedure were normal) or new, significant Q waves in at least two contiguous leads of an ECG were considered an MI. If the patient was within 24 h of CABG, an increase in CK-MB to a value at least 5 \( \times \) the ULN or new, significant Q waves in at least two contiguous leads of an ECG constituted an MI. Stroke was defined as a focal neurological deficit lasting \( > 24 \) h. Congestive heart failure was marked as an outcome, if signs and symptoms of CHF were documented in the medical record as starting at any time after the initial hospital presentation (i.e. the patient did not arrive with signs of CHF at presentation) or if clear documentation existed that the initial, presenting episode of CHF resolved and then recurred or worsened during the hospitalization. Signs/symptoms included paroxysmal nocturnal dyspnea, orthopnea, shortness of breath, or lower extremity oedema and were accompanied by at least one of the following: rales/crackles on physical exam in at least one of three of the lung fields, documented S3 heard on cardiac exam, jugular venous distension, elevated brain natriuretic peptide (BNP) or pro-BNP levels, or documented pulmonary oedema on a chest X-ray. Major bleeding was defined as any one of the following: an absolute haematocrit drop of \( \geq 12\% \) (baseline haematocrit–nadir haematocrit \( \geq 12\% \)), intracranial haemorrhage, witnessed retroperitoneal bleeding event, baseline haematocrit \( \geq 28\% \) and red blood cell transfusion, baseline haematocrit \( < 28\% \) and red blood cell transfusion and witnessed bleeding event.

**Statistical analyses**

Baseline characteristics, treatment profiles, procedure use, and clinical outcomes were compared across different numbers of vascular territories with pre-existent atherosclerotic involvement. Continuous
variables are presented as means and standard deviations, and categorical variables are expressed as frequencies and percentages. To test for trend of a patient’s baseline characteristics, in-hospital care patterns, and outcomes with respect to number of vascular territories with pre-existent atherosclerotic involvement, χ² rank correlation statistics were used for continuous variables and χ² rank-based group mean score statistics were used for categorical variables.

In examining the association between numbers of vascular territories with pre-existent atherosclerotic involvement and outcomes, multivariable logistic regression was used to estimate the marginal effects of number of vascular territories with pre-existent atherosclerotic involvement. The generalized estimating equation method was used with exchangeable working correlation structure was used to account for within-hospital clustering, because patients at the same hospital are more likely to have similar responses relative to patients at other hospitals (i.e. within-centre correlation for response). The method produces estimates similar to those from ordinary logistic regression, but the estimated variances of the estimates are adjusted for the correlation of outcomes within each hospital.

Variables adjusted in the models for in-hospital adverse events were chosen on the basis of clinical judgment. The variables were sex, white race, body mass index, age, heart rate, systolic blood pressure, family history of CAD, hypertension, diabetes mellitus, current/recent smoking, dyslipidemia, prior CHF, renal insufficiency, ST deviation, CHF, positive cardiac marker, and physician specialty. All continuous variables were fitted using linear splines with several knots. For the composite outcome, an additional logistic regression model was used to calculate the effect of number of diseased beds considering other variables listed above. In this model, all continuous variables were fitted as linear for ease of interpretation. χ² score was used to determine the significance of each variable considering other variables in the model.

Odds ratios and 95% confidence intervals for odds ratios were presented for each number of diseased beds compared with 0 diseased beds. A formal contrast was used to test whether any number of diseased beds was statistically significantly different from 0 diseased beds (three degrees-of-freedom test). All tests are two-sided, and a P-value of < 0.05 was considered significant for all tests. The potential inflation

of experiment wise Type I error due to multiple comparisons was not accounted for because this study is not experimental but only exploratory. All analyses were performed using SAS software (version 8.2, SAS Institute, Cary, NC, USA).

**Results**

Of the 95,749 patients in this analysis, 46,814 (48.9%, 95% CI 48.6–49.2%) had no known prior arterial disease before hospital presentation, 36,704 (38.3%, 95% CI 37.8–39.0%) had known prior disease in one arterial territory, 10,675 (11.2%, 95% CI 10.9–11.9%) had known arterial disease in two territories, and 1,556 (1.6%, 95% CI 1.5–1.8%) had known arterial disease in three territories. Thus, a total of 12.8% had known prior arterial disease in two or three territories, termed polyvascular disease.

The baseline characteristics of patients with greater extent of arterial disease are shown in Table 1. Greater extent of disease was significantly associated with older age, male sex, white race, lower body mass index, less smoking, and higher rates of hypertension, dyslipidemia, renal insufficiency, prior CHF, signs of CHF on admission, diminished ejection fraction among patients tested, ST-segment depression on admission, and diabetes.

Table 2 lists the medication use in the first 24 h after admission. There was significantly less use of intravenous glycoprotein IIb/IIIa inhibitors with greater extent of prior arterial disease. Table 3 lists the medications and lifestyle recommendations at discharge. Smoking cessation counselling was less frequent with greater extent of prior arterial disease. Table 4 lists the rates of procedures, which were used significantly less frequently in patients with polyvascular disease. Even after adjustment, there was a significantly lower rate of catheterization, PCI, and CABG in patients with polyvascular disease (data not shown). This was true despite

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**Table 3** Medication use and lifestyle recommendations at discharge in groups with 0, 1, 2, or 3 vascular territories with pre-existent atherosclerotic involvement

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (%)</td>
<td>40.071 (94.4)</td>
<td>30.818 (94.4)</td>
<td>85.14 (93.1)</td>
<td>1199 (92.7)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>37.658 (90.6)</td>
<td>29.983 (92.1)</td>
<td>85.54 (92.7)</td>
<td>1227 (92.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipid-lowering agent (%)</td>
<td>24.872 (87.6)</td>
<td>22.169 (88.6)</td>
<td>63.14 (87.6)</td>
<td>950 (86.3)</td>
<td>0.0741</td>
</tr>
<tr>
<td>ACE-inhibitor (%)</td>
<td>18.374 (63.1)</td>
<td>17.644 (64.9)</td>
<td>52.51 (67.8)</td>
<td>770 (71.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clopidogrel (%)</td>
<td>28.391 (70.1)</td>
<td>22.795 (73.2)</td>
<td>63.41 (73.4)</td>
<td>931 (76.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac rehabilitation referral (%)</td>
<td>25.222 (64.7)</td>
<td>16.690 (58.6)</td>
<td>42.99 (57.0)</td>
<td>590 (58.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diet modification counselling (%)</td>
<td>37.615 (83.2)</td>
<td>28.234 (80.3)</td>
<td>79.46 (79.4)</td>
<td>1161 (80.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking cessation counselling (%)</td>
<td>12.267 (86.6)</td>
<td>7.029 (82.0)</td>
<td>18.06 (78.1)</td>
<td>23.9 (73.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme.

**Table 4** Procedural use in groups with 0, 1, 2, or 3 vascular territories with pre-existent atherosclerotic involvement

<table>
<thead>
<tr>
<th></th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac catheterization (%)</td>
<td>37.119 (89.4)</td>
<td>25.126 (85.3)</td>
<td>60.61 (81.1)</td>
<td>80.1 (80.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiac catheterization in 48 h (%)</td>
<td>30.927 (74.5)</td>
<td>19.073 (64.7)</td>
<td>41.20 (55.1)</td>
<td>54.1 (54.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percutaneous coronary intervention (%)</td>
<td>22.656 (54.6)</td>
<td>14.386 (48.8)</td>
<td>32.31 (43.2)</td>
<td>40.2 (40.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percutaneous coronary intervention in 48 h (%)</td>
<td>19.211 (46.3)</td>
<td>10.927 (37.1)</td>
<td>21.92 (29.3)</td>
<td>25.9 (26.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (%)</td>
<td>61.01 (14.7)</td>
<td>29.61 (10.1)</td>
<td>60.2 (8.1)</td>
<td>60.6 (6.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Figure 2** A comparison of in-hospital outcomes for those with 0, 1, 2, or 3 prior vascular territories involved. CHF, congestive heart failure; MI, myocardial infarction.
the fact that patients with polyvascular disease had a significantly higher prevalence of triple-vessel CAD (in those who underwent catheterization): 23.2, 36.1, 43.3, and 50.4%, respectively, for 0, 1, 2, or 3 prior arterial territories involved (P < 0.0001).

With increasing degrees of prior known arterial involvement (0, 1, 2, 3), there was a significant increase in the rates of death (3.4, 4.2, 6.3, 7.3%, respectively; P < 0.0001), MI (1.9, 2.3, 3.2, 3.2%, respectively; P < 0.0001), stroke (0.6, 0.8, 0.9, 1.4%, respectively; P < 0.0001), CHF (5.8, 8.4, 12.3, 14.9%, respectively; P < 0.0001), and the composite (9.9, 13.4, 18.9, 21.9%, respectively; P < 0.0001) (Figure 2). There was also a significant increase in the rates of transfusion among non-CABG patients (7.0, 10.0, 14.7, 17.1%, respectively; P < 0.0001) (Figure 3).

Figure 4 presents the adjusted outcomes, demonstrating a graded increase in risk of ischaemic events as well as transfusion, moving from 1 to 2 to 3 prior arterial territories involved compared with 0 arterial territories involved. The adjusted rates of major bleeding were not significantly different with greater arterial territory involvement. Table 5 presents the multivariate model for the composite outcome of death/MI/stroke/CHF. The odds ratios associated with 1, 2, or 3 prior arterial territories (compared with 0) for composite in-hospital ischaemic events were 1.07, 1.26, and 1.31, respectively (P < 0.001). The c-index for the model was 0.74. With an increasing number of vascular beds involved (vs. none), there was a significant, graded increase in risk. Additionally, polyvascular disease (two or three prior arterial territories involved vs. 0 or 1) was associated with a significantly higher risk for the composite of in-hospital ischaemic events, with an odds ratio of 1.22.

Discussion

The present analysis of the CRUSADE registry finds that ~13% of patients presenting with high-risk NSTE ACS have prior known arterial disease in two or three territories. Such patients with polyvascular disease were found to have a greater degree of cardiovascular risk factors and a higher rate of in-hospital mortality, MI, stroke, and CHF. Even after adjusting for the greater prevalence of risk factors, prior polyvascular disease was found to be an
independent predictor of in-hospital ischaemic events, with an odds ratio greater than that associated with diabetes mellitus. Additionally, the presence of polyvascular disease was independently associated with a higher rate of transfusions. There was less use of certain guideline-recommended, evidence-based therapies, even in the absence of contraindications, in patients with polyvascular disease. Smoking cessation, for example, was recommended significantly less often in patients with polyvascular disease. Use of cardiac catheterization, PCI, and CABG was also suboptimal in patients with polyvascular disease, even after adjustment for their greater extent of comorbidities.

The REducation of Atherothrombosis for Continued Health (REACH) registry found a prevalence of ~15% polyvascular disease in stable outpatients with atherothrombosis or multiple risk factors for atherothrombosis. The present analysis of the CRUSADE registry finds ~13% prior polyvascular disease in patients with ACS. In both analyses, the patients with polyvascular disease had a significantly higher rate of ischaemic events. A post hoc analysis of Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) also showed that patients with polyvascular disease had markedly elevated event rates and additionally identified a potentially large benefit of dual antiplatelet therapy in this cohort.18,19 Likely, risk factor modification and aggressive medical therapy are particularly important in patients with manifest polyvascular disease. Under-treatment of patients with PAD or CVD who present with ACS may also account, in part, for the observed worse outcomes seen in this analysis.20,21 The present analysis shows that patients with polyvascular disease are less likely to get certain evidence-based therapies, despite their higher-risk profiles and even in the absence of contraindications. Lower rates of revascularization in patients with polyvascular disease—despite their presenting with more triple-vessel coronary artery disease, left ventricular dysfunction, and ST-segment depression—may in part explain their worse observed outcomes. Of course, some of the lower rate of revascularization may have been due to appropriate concern about comorbidities. Because patients with polyvascular disease also had a higher incidence of transfusion, careful assessment of individual patient risk—benefit is necessary. Nevertheless, this treatment gap presents an opportunity for quality improvement by identifying patients with polyvascular disease and intensifying their care. In the context of clinical trials, patients with polyvascular disease may represent an appealing population for study due to their high event rates.

Functional impairment is a problem for patients with PAD.22 Potentially, functional impairment in patients with PAD may keep them from ambulating to the point of having angina. Therefore, patients with PAD may present with much more advanced coronary atherosclerosis, as they lack an early warning system that is available to patients with good exercise capacity who experience angina.

Rates of transfusion were also higher in patients with polyvascular disease. In part, this may have to do with vascular access that is more complicated due to PAD involving the femoral arteries. Of course, the greater prevalence of multiple associated risk factors for bleeding such as age and renal insufficiency in patients with polyvascular disease may also account for part of the higher transfusion rates. Polyvascular disease, however, remained a predictor of transfusion even after adjusting for these potential confounders. Protocol-defined major bleeding, perhaps a more objective measure of bleeding than transfusions, was higher in patients with polyvascular disease on unadjusted analyses but not after adjustment.

There are certain limitations to this analysis. Misclassification bias of PAD patients may have been possible, as PAD is known to be underdiagnosed.3,23 The only criterion for CVD was a history of prior stroke, which may have also led to misclassification. However, any such misclassification would have likely biased the results towards the null. Additionally, it would have been interesting to have longer-term outcomes available to assess the impact of polyvascular disease over time, although the REACH database has already provided this information to an extent.

In conclusion, prior polyvascular disease is present in ~13% of patients presenting with NSTE ACS and is an independent predictor of ischaemic outcomes, perhaps reflecting the degree of atherothrombotic burden. Additionally, polyvascular disease independently predicts transfusion, though not more objectively defined major bleeding. Future efforts should be directed towards better identification of patients with polyvascular

### Table 5 Factors associated with the composite outcome of in-hospital death, myocardial infarction, stroke, or congestive heart failure

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>χ²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.26</td>
<td>1.24, 1.28</td>
<td>605</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (per 10 mm Hg)</td>
<td>0.94</td>
<td>0.93, 0.94</td>
<td>295</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Signs of CHF</td>
<td>2.32</td>
<td>2.06, 2.61</td>
<td>195</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.31</td>
<td>1.25, 1.37</td>
<td>119</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive cardiac marker</td>
<td>1.94</td>
<td>1.69, 2.24</td>
<td>84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (per 10 b.p.m.)</td>
<td>1.04</td>
<td>1.04, 1.05</td>
<td>83</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (per 10 mm Hg)</td>
<td>0.94</td>
<td>0.93, 0.95</td>
<td>165</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transient ST-elevation</td>
<td>1.32</td>
<td>1.25, 1.38</td>
<td>68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both</td>
<td>1.49</td>
<td>1.24, 1.79</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes</td>
<td>1.16</td>
<td>1.11, 1.20</td>
<td>48</td>
<td>&lt;0.001</td>
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<tr>
<td>Polymorphous disease</td>
<td></td>
<td></td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One vascular bed</td>
<td>1.07</td>
<td>1.02, 1.12</td>
<td></td>
<td></td>
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<tr>
<td>Two vascular beds</td>
<td>1.26</td>
<td>1.19, 1.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three vascular beds</td>
<td>1.31</td>
<td>1.17, 1.48</td>
<td></td>
<td></td>
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<tr>
<td>Dyslipidemia</td>
<td>0.88</td>
<td>0.85, 0.92</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>1.23</td>
<td>1.15, 1.32</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.91</td>
<td>0.87, 0.94</td>
<td>25</td>
<td>&lt;0.001</td>
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<tr>
<td>Cardiologist</td>
<td>0.86</td>
<td>0.81, 0.92</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.08</td>
<td>1.03, 1.12</td>
<td>11</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Other variables in the model were current/recent smoker, family history of coronary artery disease, white ethnicity, and body mass index. b.p.m., beats per minute; CHF, congestive heart failure; CI, confidence interval; SBP, systolic blood pressure.

*p-values for multilevel variables were calculated in formal contrasts which tested if any level is statistically significant.

bZero vascular beds is the reference group.
disease and targeted therapies to reduce their excess risk. Patients with polyvascular disease may represent a population for intensive secondary prevention, both in clinical trial and real world populations.

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References


CARDIOVASCULAR FLASHLIGHT

Transient mid-ventricular ballooning cardiomyopathy associated with bladder pheochromocytoma

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A 45-year-old woman with no cardiac history was admitted for hematuria. A computed tomography scan revealed polypoid-enhancing mass protruding from the bladder dome to lumen (Panel A). Transurethral resectional biopsy of bladder tumour was performed under the general anaesthesia. During the procedure, the oxygen saturation dropped, and the ECG showed sinus tachycardia with T-wave inversion in leads V2–V6. Chest X-ray showed newly developed cardiomegaly with pulmonary oedema. The troponin I level was mildly elevated. The trans-thoracic echocardiography revealed akinesis of the mid-ventricle with a hypercontractile apex and base. Emergency coronary angiography showed normal epicardial coronary arteries. Left ventriculography demonstrated a ballooning of mid-ventricular segments without apical and basal involvement (Panel B). The histological finding has revealed the bladder tumour to be the pheochromocytoma. Immunohistochemical staining shows catecholamine expression on cytoplasmic granules (DAB, ×200; Panel C). Echocardiography repeated on Day 21 after surgery showed a normal left ventricular systolic function without wall motion abnormalities. On Day 32 of diagnosis, partial cystectomy was performed. The patient has not experienced any subsequent cardiac events afterwards for 5 months.

There already have been reports of Takotsubo cardiomyopathy or inverted Takotsubo cardiomyopathy associated with pheochromocytoma. However, this case is the first report of the transient mid-ventricular ballooning patterned stress-induced cardiomyopathy induced by pheochromocytoma, which developed in bladder, the extra-adrenal system.

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