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Frailty measures, inflammatory biomarkers and post-operative complications in older surgical patients

SIR—The syndrome of frailty is a state of increased vulnerability towards stressors in older individuals, leading to an heightened risk of experiencing adverse health outcomes [1]. An operational definition is the one-dimensional physical ‘frailty phenotype’, which includes the presence of at least three of the following five criteria: unintentional weight loss, exhaustion, muscle weakness, slow walking speed and reduced physical activity [2].

A different tool to detect vulnerability in older patients is the Comprehensive Geriatric Assessment (CGA)—a multidimensional evaluation of health status including comorbidity, polypharmacy, physical functioning, nutritional and cognitive status, depression and social support. Based on a CGA, patients may be categorized into groups of fit, intermediate or frail [3]. CGA may uncover potentially remediable medical problems with implications for treatment, prognosis and rehabilitation [4–6]. We have previously shown that a CGA-based frailty measure predicts postoperative complications in older patients undergoing surgery for colorectal cancer [7].

An important aspect of the pathophysiology of frailty seems to be dysregulation of inflammatory pathways and of the coagulation system [1]. Thus, measuring circulating biomarkers might contribute to the clinical diagnosis of frailty. Higher serum levels of the acute-phase protein C-reactive protein (CRP), as well as the inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), have been associated with reduced physical function and different frailty measures [8–13]. Increased levels of plasma D-dimer, a marker of ongoing coagulation and fibrinolysis, have also been linked to these outcomes [8, 11].

The purpose of this study was to compare levels of inflammatory biomarkers (CRP, IL-6, TNF-α), and D-dimer in elderly colorectal cancer patients classified according to a modified version of the physical frailty phenotype and according to a CGA. We further wanted to investigate the predictive value of the individual biomarkers for the development of post-operative complications [7].

Materials and methods

This was a substudy of a prospective study designed to explore whether CGA frailty predicted post-operative complications in elderly patients with colorectal cancer [7]. The Regional Committee for Medical and Health Research Ethics in Eastern Norway approved the study. Patients provided a written informed consent.

Eligible participants were inpatients from three public hospitals in Norway (Ullevål, Aker and Akershus University Hospitals), 70 years and older, undergoing elective resections of tumours in colon or rectum. A physician trained in geriatrics performed a pre-operative CGA, and blood samples were collected within 14 days before surgery. For details on assessment tools, frailty classifications and the analyses of blood samples, see Supplementary data available in Age and Ageing online. Information on post-operative complications was retrospectively collected from hospital records, along with information from staff, patients and caregivers. Complications were classified as minor (grade I), potentially life-threatening with (grade II) or without (grade III) sequelae or fatal (grade IV) based on the grading system developed by Clavien et al. [14]. Details on this are given in Supplementary data available in Age and Ageing online. The outcome variables were defined as ‘severe’ (≥grade II) versus ‘no/mild’ complications (≤grade I) and ‘any’ complication versus ‘no’ complications.

Non-parametric statistics were applied due to skewed distribution of biomarkers. The D-dimer analyses had a lower detection level of 0.04 mg/l and measurements below threshold were given this value.

To examine differences in the levels of the various biomarkers within each frailty measure, the Kruskal–Wallis test was used. When overall significant differences (P < 0.05) were found, we performed Mann–Whitney U tests between group pairs, adjusting the statistical level of significance to 2.5% using the Bonferroni correction.

We grouped levels of individual biomarkers into quartiles or tertiles and examined their association with post-operative complications by chi-square tests. Trend analyses were performed to identify cut-off points. CRP-levels were dichotomized into values below the 25th percentile versus higher levels and IL-6 into values below the 66.66th percentile versus higher levels. The dichotomized variables were subsequently included in crude and adjusted logistic
regression models to examine their relative predictive value for post-operative complications.

All analyses were performed with SPSS 16.0 software (Chicago, IL, USA).

**Results**

A total of 187 patients were recruited, and blood was collected from 137. Median age was 80 years and 69% had colon cancer. Further patient characteristics are shown in Supplementary data available in *Age and Ageing* online.

Levels of biomarkers by the physical frailty phenotype and CGA-category are shown in Table 1. Overall significant differences within the physical frailty phenotype were found for concentrations of CRP (*P* = 0.001), IL-6 (*P* < 0.001), TNF-α (*P* = 0.004) and D-dimer (*P* = 0.031). The frail group had significantly higher levels of CRP and IL-6 than the pre-frail group (*P* < 0.025). The same pattern was not found for TNF-α, where the pre-frail group demonstrated higher levels of this biomarker than the robust group (*P* < 0.025).

The same overall differences across groups were present between the CGA categories. Furthermore, CRP and IL-6 concentrations were significantly higher in the intermediate group compared with the fit group, and in the frail group compared with the intermediate group (*P* < 0.025). TNF-α levels were also significantly higher in frail than in intermediate patients.

In crude logistic regression analyses, levels of CRP above the lower quartile were significantly associated with both ‘any’ (OR 2.18, 95% CI 1.0–4.75) and ‘severe’ (OR 2.60, 95% CI 1.13–5.96) complications, whereas levels of IL-6 above the 66.66th percentile were associated with ‘severe’ complications (OR: 2.4, 95% CI: 1.14–5.06).

Results from multivariable analyses adjusted for tumour location (an established risk factor for developing post-operative complications) and CGA frailty are presented in Table 2. Whereas CGA frailty proved to be a strong independent predictor for both any complication and severe complications, as previously shown [7], IL-6 was the only biomarker with a predictive value for severe complications.

**Discussion**

When comparing levels of biomarkers between patients classified according to an approximation to the physical frailty phenotype and a CGA, we found overall differences

### Table 1. Comparison of biomarkers by the physical frailty phenotype and CGA category

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Robust/fit</th>
<th>Pre-frail/intermediate</th>
<th>Frail</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>IQR</td>
<td>Median</td>
<td>IQR</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty phenotype</td>
<td>4.30 2.68–8.73</td>
<td>5.80 3.0–12.44</td>
<td>15.40** 5.80–19.88</td>
<td>0.001</td>
</tr>
<tr>
<td>CGA category</td>
<td>2.95 0.95–4.98</td>
<td>4.50* 3.0–10.80</td>
<td>8.20** 4.60–16.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 (pg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty phenotype</td>
<td>4.11 2.83–5.84</td>
<td>4.46 2.87–8.79</td>
<td>11.08** 5.04–13.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CGA category</td>
<td>2.60 1.40–3.30</td>
<td>4.26* 2.87–6.71</td>
<td>6.01** 3.85–10.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TNF-α (pg/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty phenotype</td>
<td>1.37 0.70–2.22</td>
<td>2.19* 1.10–3.00</td>
<td>2.11 1.39–3.90</td>
<td>0.004</td>
</tr>
<tr>
<td>CGA category</td>
<td>0.88 0.64–2.11</td>
<td>1.49 0.88–2.39</td>
<td>2.28** 1.29–3.57</td>
<td>0.001</td>
</tr>
<tr>
<td>D-dimer (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty phenotype</td>
<td>0.60 0.40–1.00</td>
<td>0.70 0.60–1.20</td>
<td>1.30 0.65–2.45</td>
<td>0.031</td>
</tr>
<tr>
<td>CGA category</td>
<td>0.55 0.33–1.00</td>
<td>0.60 0.30–1.10</td>
<td>0.80 0.50–1.50</td>
<td>0.035</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

*For difference between groups, by the Kruskal–Wallis test.

**Significantly different from fit/robust group, *P* < 0.025 by the Mann–Whitney test.

**Significantly different from intermediate/pre-frail group, *P* < 0.025 by the Mann–Whitney test.

### Table 2. Predictors of postoperative complications

<table>
<thead>
<tr>
<th></th>
<th>Any complication</th>
<th>Severe complications</th>
<th>95% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP &gt; 25th percentile (reference: 25th percentile)</td>
<td>1.58</td>
<td>0.68–3.71</td>
<td>2.04</td>
<td>0.84–4.97</td>
</tr>
<tr>
<td>CGA frailty (reference: non-frail)</td>
<td>3.99</td>
<td>1.77–9.03</td>
<td>3.06</td>
<td>1.44–6.51</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 &gt;66.66th percentile (reference: &lt;66.66th percentile)</td>
<td>2.21</td>
<td>0.91–5.37</td>
<td>2.40</td>
<td>1.14–5.06</td>
</tr>
<tr>
<td>CGA frailty (reference: non-frail)</td>
<td>4.16</td>
<td>1.79–9.68</td>
<td>3.06</td>
<td>1.40–6.69</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.

*Models adjusted by tumour location.
Research letters

in the levels of CRP, IL-6, TNF-α and D-dimer. Levels of CRP and IL-6 were significantly higher in frail compared with non-frail patients within both measures. For CGA frailty, even the levels of TNF-α were significantly increased. In addition, we found the inflammatory biomarker IL-6 to be an independent predictor of severe complications after surgery for colorectal cancer.

Our findings are in accordance with previous studies. In the Cardiovascular Health Study, higher levels of CRP were reported in frail patients [11], and Hubbard et al. [9] have shown that inflammatory activity is higher in frail than in non-frail patients across different frailty measures. Our paper is unique in demonstrating differences in inflammatory markers between frail and non-frail patients with the same index disease.

We have previously reported that frailty according to a CGA, but not increasing age, predicts post-operative complications in older patients with colorectal cancer [7]. Higher levels of both CRP and IL-6 also predicted complications, but when CGA frailty was included in multivariate models, the independent explanatory value of biomarkers was significantly reduced. This indicates that the frailty measure derived from CGA comprises aspects other than systemic inflammation with importance to developing complications and highlights the value of including frailty measures in studies of geriatric surgery. Interestingly, high levels of IL-6 remained independently predictive of severe complications in the adjusted analyses.

There are some limitations to our study. Biomarkers were measured in one sample from each patient, not accounting for physiological fluctuations in peripheral blood. D-dimer analyses were performed at different laboratories, which may have caused inconsistencies.

The study sample was part of a prospective study [7]. Originally, the cohort consisted of 187 patients, and blood samples were obtained from 137. This was due to practical circumstances: the patients were recruited from different hospitals, and it was not always possible to communicate the need of additional samples.

As we used an approximation to the frailty criteria developed by Fried et al., the results should be interpreted with caution. Only patients with colorectal cancer were included, and the results may not apply to surgical patients in general. Furthermore, the sample size is relatively small, and our findings need to be validated in larger cohorts.

Previous studies investigating the clinical consequences of increased inflammatory activity in older adults have focused on the development of disability and risk of mortality. An important strength of our study is that we have been able to link higher levels of inflammatory biomarkers in a well-described older cohort to short-term adverse outcomes after exposure to physical stress, i.e. a surgical procedure. Further studies are needed to investigate biomarkers as an addition to clinical frailty measures in pre-operative assessment of older patients. Meanwhile, our aim should be to provide optimal peri-operative care to high-risk elderly surgical patients as this may reduce the risk of post-operative complications.

Key points

- Frail older patients with colorectal cancer have higher pre-operative levels of the inflammatory markers CRP and IL-6.
- IL-6 is an independent predictor of post-operative complications when adjusting for tumour location and frailty.
- Biomarkers may add validity to a CGA in the pre-operative risk assessment of older surgical patients.

Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References

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