BMJ Open

Impact of multimorbidity on long-term outcomes in older adults with non-ST elevation acute coronary syndrome in the North East of England: a multi-centre cohort study of patients undergoing invasive care

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To cite: Beska B, Mills GB, Ratcovich H, *et al*. Impact of multimorbidity on long-term outcomes in older adults with non-ST elevation acute coronary syndrome in the North East of England: a multi-centre cohort study of patients undergoing invasive care. *BMJ Open* 2022;**12**:e061830. doi:10.1136/bmjopen-2022-061830

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-061830).

Received 08 February 2022
Accepted 15 July 2022

Check for updates

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ABSTRACT

Objectives Older adults have a higher degree of multimorbidity, which may adversely affect longer term outcomes from non-ST elevation acute coronary syndrome (NSTE-ACS). We investigated the impact of multimorbidity on cardiovascular outcomes 5 years after invasive management of NSTE-ACS.

Design Prospective cohort study.

Setting Multicentre study conducted in the north of England.

Participants 298 patients aged ≥75 years with NSTE-ACS and referred for coronary angiography, with 264 (88.0%) completing 5-year follow-up.

Main outcome measures Multimorbidity was evaluated at baseline with the Charlson comorbidity index (CCI). The primary composite outcome was all-cause mortality, myocardial infarction, stroke, urgent repeat revascularisation or significant bleeding.

Results Mean age was 80.9 (±6.1) years. The cohort median CCI score was 5 (IQR 4–7). The primary composite outcome occurred in 48.1% at 5 years, at which time 31.0% of the cohort had died. Compared with those with few comorbidities (CCI score 3–5), a higher CCI score (≥6) was positively associated with the primary composite outcome (adjusted HR (aHR) 1.64 (95% CI 1.14 to 2.35), p=0.008 adjusted for age and sex), driven by an increased risk of death (aHR 2.20 (1.38 to 3.49), p=0.001). For each additional CCI comorbidity, on average, there was a 20% increased risk of the primary composite endpoint at 5 years (aHR 1.20 (1.09 to 1.33), p<0.001).

Conclusions In older adults with NSTE-ACS referred for coronary angiography, the presence of multimorbidity is associated with an increased risk of long-term adverse cardiovascular events, driven by a higher risk of all-cause mortality.

Trial registration number NCT01933581; ClinicalTrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study includes older, mainly frail or prefrail, multimorbid, high-risk patients who are usually excluded from cardiovascular research.

⇒ This study is a cohort study with a long prospective follow-up, with previous studies on the subject either being registry studies, studies with shorter follow-up or studies of younger adults.

⇒ All patients in the current study had already been referred for coronary angiography after presenting with non-ST elevation acute coronary syndrome at the referring hospital; therefore, we do not capture patients who are treated with a conservative strategy.

INTRODUCTION

The older adult population has an increasing incidence of acute coronary syndrome (ACS),[1] particularly non-ST elevation ACS (NSTE-ACS).[2] The presentation and management of ACS in older adults can be complex, especially in the context of multimorbidity, which is the presence of two or more chronic medical conditions.[3] The prevalence of multimorbidity is increasing due to successful public health lifestyle campaigns and improved disease survival.[4] In the UK, over 97% of older adults with cardiovascular disease have one additional chronic health condition, and over 70% of patients have three or more.[5]

The European Society of Cardiology (ESC) and American Heart Association both recommend an individualised management approach in older patients.[6 7] Multimorbidity has been shown to be associated with adverse outcomes in patients with NSTE-ACS up to 3 years.[8 9] However, we lack data to inform the optimal management strategy and longer term prognosis of older adults with multimorbidity that present with NSTE-ACS and receive an invasive management strategy.[10–13] ESC guidelines highlight this important gap in evidence.[6] As the population ages, the proportion of these older patients with multiple chronic conditions and ACS will continue to increase, and data are needed to inform decision-making and discussions with patients and their families.

We hypothesised that more significant multimorbidity was associated with an increased incidence of the primary composite outcome. In this study, we examined the association between multimorbidity and long-term outcomes in older adults presenting with NSTE-ACS who underwent an invasive management strategy, in a prospective cohort study.

METHODS

Study design

This is an extended follow-up analysis of The **I**mprove **C**ardiovascular **O**utcomes in High Risk PatieN**t**s with Acute Coronary Syndrome (ICON1) study, a multicentre prospective cohort study of older patients with NSTE-ACS treated with an invasive management strategy. The study protocol has been described previously,[14] and myocardial infarction was defined by the universal definition of myocardial infarction.[15] ICON1 study recruitment began in 2012 and ended in 2016, with this 5-year extension to follow-up completing in 2021. The study was prospectively registered with the UK Clinical Research Network (UKCRN ID 12742) and ClinicalTrials.gov.

Patient and public involvement

This analysis was conducted without any direct patient or Public involvement.

Study population

Three hundred older patients with NSTE-ACS who were referred for invasive angiography at two high-volume percutaneous coronary intervention (PCI) centres: Freeman Hospital, Newcastle on Tyne (receiving patients referred from six district hospitals, annual PCI procedure volume approximately 3000 cases) and James Cook University Hospital, Middlesbrough (receiving patients referred from five district hospitals, annual PCI procedure volume approximately 2500 cases) were recruited between November 2012 and December 2015 reflecting the population of the North of England.[10] All patients underwent coronary angiography and received guideline-recommended management of NSTE-ACS. Exclusion criteria were cardiogenic shock, primary arrhythmia, coexisting significant valvular heart disease, malignancy with life expectancy ≤1 year, active infection and inability to provide informed consent. Patients with alternative diagnoses after coronary angiography were excluded.

Clinical data collection and assessment of multi-morbidity

Baseline data collection occurred during index presentation and included patient demographics and medical history by members of the cardiovascular research team consisting of principal investigators, research fellows and research nurses. Laboratory blood tests were collected at the time of coronary angiography and results were obtained from the electronic medical record. Angiographic details including arterial access site, procedural details, stent types were collected from the catheter laboratory reports. Medications prescribed at discharge from index hospitalisation were recorded from electronic hospital records. Participants were evaluated for frailty using the Fried criteria consisting of subjective and objective assessment of slowness, weakness, low physical activity, exhaustion and weight loss. Patients were considered robust if no criteria were met, prefrail if one or two criteria were met and frail if three or more criteria were met.[16]

Multimorbidity was assessed by experienced members of the research team using the Charlson comorbidity index (CCI) at baseline, a weighted index taking into account age and medical conditions.[17] The overall CCI score is a sum of the scores for specified comorbidities and age. The score ranges from 0 to 37. Due to the age criterion (three points for age 70–79 years) and the study age inclusion criteria (≥75 years), the minimum CCI score of study participants was 3. There is no universally accepted cut point for the measurement of multimorbidity. Previous studies that predominately included younger patients used a CCI cut point of three to dichotomise (with a minimum included CCI of 0).[18–20] Therefore, in the cohort of older, frail patients included in this study in which three is the cohort minimum score, the cut-off was set at 3 above the minimum cohort score, so participants were stratified into two groups for analysis: CCI 3 to 5 and CCI ≥6.

Outcomes and follow-up

Five-year follow-up data were collected using the Summary Care Records (SCR), National Health Service Digital and tertiary centre hospital electronic patient records. SCR is an electronic record of important patient information, created from primary care physician medical records. The primary outcome was a composite of all-cause mortality, myocardial infarction, stroke or transient ischaemic attack, repeat unplanned revascularisation and significant bleeding (defined as Bleeding Academic Research Consortium type 2 or greater).[10] In participants where more than one component of the composite outcome occurred, time-to-first-event was used and all patients were censored at 5 years. The individual elements of the primary composite outcome were analysed separately as secondary outcomes.

Statistical analysis

Categorical data were analysed with X^2 test where all predicted counts were higher than five. The distribution of variables was assessed using the Shapiro-Wilk test, with normality defined as p>0.05. Normally distributed variables are presented as mean and SD (±) and were compared using independent samples test. Non-normally distributed variables are presented as median with IQR and compared using the Kruskall-Wallis one-way test of variance.

Kaplan-Meier survival analysis was performed to analyse the impact of multimorbidity on the incidence of the primary composite outcome at 5 years, with the Log-rank test for a statistically significant difference. Cox proportional HR was used to investigate the relationship between CCI and the incidence of the primary composite outcome at 5 years. HRs with 95% CIs are reported. Three *a priori* models were constructed. Model 1 is an unadjusted univariate analysis. Model 2 was a multivariate analysis adjusted for age and sex. Model 3 was a multivariate analysis adjusted for age, sex and management strategy. A post hoc model was constructed to additionally control for Global Registry of Acute Coronary Events (GRACE) 2.0 score (model 4).

To analyse the additive impact of increasing CCI score, a Cox proportional hazards regression model was used with CCI inputted as an ordinal variable, adjusted for age and sex. Statistical analysis was performed using SPSS Statistics V.27 (IBM Corporation). Statistical significance was defined as p<0.05.

RESULTS

Baseline characteristics

Overall, 264 patients (88.0%) out of the total 300 patients completed 5-year follow-up and are included in this extended follow-up analysis (figure 1). Of the total cohort, 15 patients (5.4%) were lost to follow-up: 12 patients (4.3%) withdrew consent and 3 patients (1.1%) had inaccessible medical records. The median CCI score was 5 (IQR 4–7, range 3 to 10) (online supplemental figure 1). The modal CCI score was 4 (25.0%). The mean age was 80.9 (±6.1) years, and 102 patients (38.6%) were women (table 1). A total of 217 patients (82.5%) were either frail or prefrail. The burden of cardiovascular risk factors was higher in those with a CCI ≥6 compared with those with a CCI 3–5. The most prevalent risk factors were hypercholesterolaemia (n=72, 69.2% vs n=80, 50.0%; p=0.002) and previous PCI (n=28, 26.9% vs n=26 (16.3%); p=0.043). There was no difference in the length of hospital stay in those with CCI ≥6 compared with those with a CCI 3 to 5 (6.5 (IQR 5–9) days vs 6.0 (4–8) days, p=0.052). Those with CCI ≥6 had significantly lower mean values of haemoglobin, higher mean creatinine, lower estimated glomerular filtration rate and higher serum glucose compared with those with CCI 3 to 5 (p<0.001 for all).

There was little difference in prescription rates in cardiovascular medications at discharge from index hospitalisation between those with a CCI ≥6 and those with a CCI 3 to 5 (p>0.05, online supplemental table 1), other than a higher rate of long-acting nitrate (n=43, 41.3% vs n=31, 19.4%, p<0.001) and nicorandil (n=24, 23.1% vs n=19, 11.9%, p=0.02) in the patients with more multi-morbidity.

Clinical presentation, procedural and angiographic characteristics

Of 212 patients (80.3%) presented with non-ST elevation myocardial infarction and 52 (19.7%) with unstable angina (table 2). Following diagnostic coronary angiography, 220 patients (83.3%) underwent PCI, 7 patients (2.7%) had coronary artery bypass grafting and 37 patients (14.0%) received medical management alone. There was no difference in the management strategy between those with CCI ≥6 and with a CCI 3 to 5 (p>0.05). There was no difference in the arterial access route (p=0.173), incidence of single-vessel (p=0.299) or multi-vessel PCI (p=0.772) between those with CCI ≥6 versu those with a CCI 3 to 5. A significantly higher proportion of patients with a CCI ≥6 received left main stem PCI compared with those with a CCI 3 to 5 (n=12, 11.5% vs n=5, 3.1%; p=0.007).

Outcome analysis

The primary composite outcome occurred in 127 patients (48.1%) at 5 years (table 3). Those with CCI ≥6 had a significantly higher incidence of the primary composite outcome compared with those with a CCI 3 to 5 (n=65, 62.5% vs n=62, 38.8%, p<0.001). At 5 years, 82 patients (31.0%) had died, with a significantly higher mortality among those with a CCI ≥6 compared with those with a CCI 3 to 5 (n=49, 47.1% vs n=33, 20.6%; p<0.001).

On average, participants with a CCI score ≥6 had double the risk of the primary composite outcome compared with CCI score 3–5 (HR 2.09, 95% CI 1.47 to 2.96, p<0.001, table 4). This remained significant when adjusted for age and sex (HR 1.67, 95% CI 1.16 to 2.40, p=0.005), and when further adjusted for management strategy (HR 1.64, 95% CI 1.14 to 2.35, p=0.007) and GRACE 2.0 score (HR 1.68, 95% CI 1.14 to 2.47, p=0.009).

The Kaplan-Meier cumulative event-free survival curve showed significant difference in the primary composite outcome at 5 years between participants scoring CCI ≥6 versus CCI 3 to 5 (p<0.001, figure 2). In a truncated analysis, the curves separate at around 200 days (online supplemental figure 2).

The secondary outcome analysis detailed the association between CCI and each individual component of the primary composite outcome (online supplemental tables 2 and 3). Participants with CCI score ≥6 had an almost threefold increased risk of mortality compared with CCI score 3–5 (HR 2.83, 95% CI 1.82 to 4.41, p<0.001), a relationship that remained significant after adjustment for age, sex and management strategy (HR 2.20, 95% CI 1.38 to 3.49, p=0.001). There was no statistically significant association between CCI category (3–5 vs CCI ≥6) and the occurrence of myocardial infarction, stroke, unplanned repeat revascularisation or significant bleeding.

After adjustment for age and sex, there was on average, a 20% increased risk of the primary composite endpoint for each additional CCI comorbidity (HR 1.20, 95% CI 1.09 to 1.33, p<0.001), and a 31% increased risk of

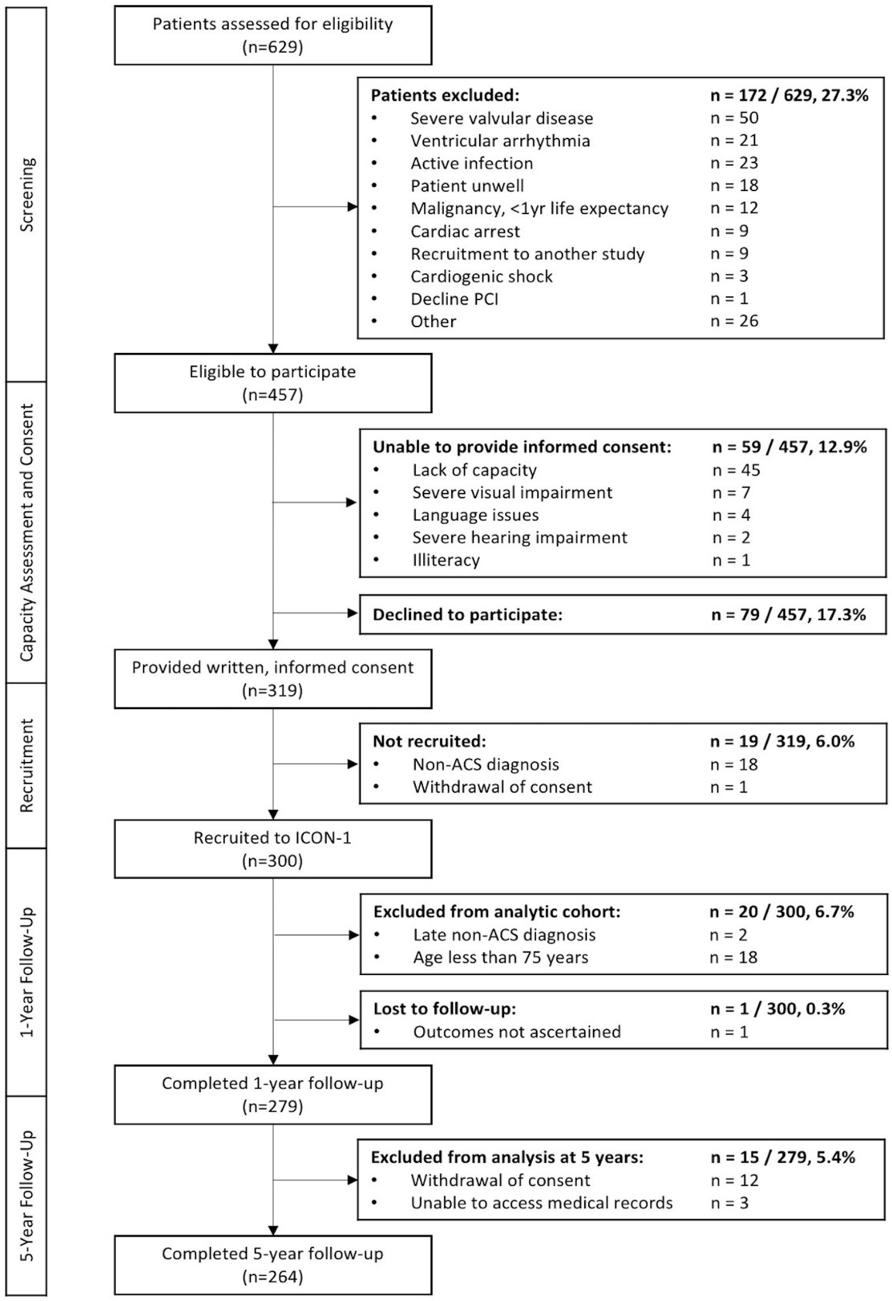

Figure 1 Flow diagram of ICON1 screening, recruitment and 5 year follow-up. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

mortality for each additional comorbidity (HR 1.31, 95% CI 1.16 to 1.47, p<0.001).

DISCUSSION

This 5-year follow-up extension to the ICON1 study provides the longest prospective follow-up of the impact of multimorbidity on outcomes after invasive management of NSTE-ACS in older adults. There are several key findings. In this cohort, there was a high level of multimorbidity among older adults undergoing invasive management of NSTE-ACS. The overall 5-year all-cause mortality in those with the highest burden of multimorbidity (CCI ≥6) approached 50%. Multimorbidity was strongly associated with an increased risk of the composite primary outcome, predominantly driven by an increased risk of mortality. In a stepwise way, with each additional comorbidity, the average risk of the primary composite outcome increased by 20%, and mortality by 31%.

The majority of older patients referred for invasive management of NSTE-ACS in this cohort had a significant burden of multimorbidity: almost 9 out of 10 participants had at least one additional comorbidity as defined by the index. Although studies show that cardiovascular risk factors such as hypertension, hypercholesterolaemia and diabetes are often aggressively managed, there is growing evidence to suggest that the burden of non-cardiovascular comorbidities is also important in predicting mortality.[18]

Beska B, *et al*. *BMJ Open* 2022;**12**:e061830. doi:10.1136/bmjopen-2022-061830

Table 1 Baseline characteristics stratified by CCI score

	Total (n=264)	CCI 3 to 5 (n=160)	CCI ≥6 (n=104)	P value
Demographics				
Age, years	80.9 (±6.1)	79.6 (±5.3)	82.3 (±5.4)	**<0.001**
Female, n (%)	102 (38.6)	62 (38.8)	40 (38.5)	0.962
Smoking status				
Current smoker	18 (6.8)	14 (8.8)	4 (3.8)	0.141
Ex-smoker	134 (50.8)	74 (46.3)	60 (57.7)	0.078
Never smoker	110 (41.7)	70 (43.8)	40 (38.5)	0.444
Clinical measures				
BMI, kg m^{-2}	26.9 (4.4)	26.9 (4.6)	27.0 (4.1)	0.915
GRACE 2.0 score	131.8 (19.3)	127.9 (17.7)	137.8 (20.1)	**<0.001**
NYHA III or IV, n (%)	53 (20.0)	21 (13.1)	32 (30.7)	**0.001**
CCS III or IV, n (%)	39 (14.8)	22 (13.8)	17 (16.3)	0.383
Fried Frailty score, n (%)*				
Frail	70 (26.6)	32 (20.1)	38 (36.5)	**0.008**
Pre-frail	147 (55.9)	94 (59.1)	53 (51.0)	
Robust	46 (17.5)	33 (20.8)	13 (12.5)	
Presentation and management strategy				
NSTEMI, n (%)	212 (80.3)	126 (78.8)	86 (82.7)	0.527
UA, n (%)	52 (19.7)	34 (21.3)	18 (17.3)	0.527
PCI, n (%)	220 (83.3)	137 (85.6)	83 (79.8)	0.239
CABG, n (%)	7 (2.7)	5 (3.1)	2 (1.9)	0.707
Medical management, n (%)	37 (14.0)	18 (11.3)	19 (18.3)	0.146
Length of hospital stay, day(s)	6.0(5.0)	6.0(4.0)	6.5(4.0)	0.052
Charlson co-morbidity index component, n (%)				
Liver disease	0 (0)	0 (0)	0 (0)	–
Diabetes	69 (26.1)	31 (19.4)	38 (36.5)	**0.003**
Moderate to severe renal disease	57 (21.6)	3 (1.9)	54 (51.9)	**<0.001**
Previous MI	87 (33.0)	31 (19.4)	56 (53.8)	**<0.001**
Congestive cardiac failure	24 (9.1)	3 (1.9)	21 (20.2)	**<0.001**
Peripheral vascular disease	25 (9.5)	6 (3.8)	19 (18.3)	**<0.001**
Previous cerebrovascular event	45 (17.0)	15 (9.4)	30 (28.8)	**<0.001**
Rheumatological disease	4 (1.5)	1 (0.63)	3 (2.9)	0.341
Peptic ulcer disease	14 (5.3)	5 (3.1)	9 (8.7)	0.088
COPD	51 (19.3)	22 (13.8)	29 (27.9)	**0.006**
Solid organ malignancy				
Localised	25 (9.5)	3 (1.9)	22 (21.2)	**<0.001**
Metastatic	0 (0)	0 (0)	0 (0)	–
Leukaemia	1 (0.38)	0 (0)	1 (0.96)	–
Lymphoma	0 (0)	0 (0)	0 (0)	–
Dementia	0 (0)	0 (0)	0 (0)	–
AIDS or HIV	0 (0)	0 (0)	0 (0)	–
Cardiac risk factors and past cardiac history, n (%)				
Hypertension	193 (73.1)	110 (68.8)	83 (79.8)	0.064
Hypercholesterolaemia	152 (57.6)	80 (50.0)	72 (69.2)	**0.002**
Previous angina	116 (43.9)	63 (39.4)	53 (51.0)	0.076
Previous PCI	54 (20.5)	26 (16.3)	28 (26.9)	**0.043**

Continued

Table 1 Continued

	Total (n=264)	CCI 3 to 5 (n=160)	CCI ≥6 (n=104)	P value
Previous CABG	17 (6.4)	8 (5.0)	9 (8.7)	0.306
Atrial fibrillation	40 (15.2)	20 (12.5)	20 (19.2)	0.161
Family history of IHD	77 (29.2)	50 (31.3)	27 (26.0)	0.407
Laboratory tests				
Haemoglobin, g L^{-1}	13.0 (±1.9)	13.5 (±1.9)	12.2 (±1.7)	**<0.001**
Creatinine, µmol L^{-1}	102.9 (±34.2)	92.1 (±23.5)	119.4 (±41.0)	**<0.001**
Estimated GFR, mL min^{-1} 1.73 m^{-2}	52.6 (±18.4)	57.9 (±17.9)	44.5 (±16.1)	**<0.001**
Glucose, mmol L^{-1}	6.5(3.0)	6.2(2.3)	7.4(4.6)	**<0.001**
Total cholesterol, mmol L^{-1}	4.0(1.6)	4.2(1.6)	3.9(1.7)	0.417
Peak troponin, ng L^{-1}	113.5(372.3)	121.0(415.0)	87.0(311.5)	0.588
High-sensitivity CRP, mg L^{-1}	4.0(8.0)	3.7(7.6)	4.2(8.3)	0.340

Normally distributed continuous variables are reported as mean (±SD), non-normally distributed continuous variables are reported as median (IQR). Statistically significant results (p≤0.05) are displayed in bold.
*One patient had missing Fried Frailty data.
BMI, body mass index; CABG, coronary artery bypass graft; CCI, Charlson comorbidity index; CCS, Canadian Cardiovascular Society angina score; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; GFR, glomerular filtration rate; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NYHA, New York Heart Association score; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischaemic attack.

The link between multimorbidity and adverse outcomes after ACS has been previously shown, with an incremental increase in the risk of death with increasing CCI score.[21] However, previous studies predominately included younger adults, over shorter follow-up periods, or include ST elevation myocardial infarction or elective PCI. To our knowledge, this is the first study to prospectively examine the impact of multimorbidity on long-term outcomes after invasive management of NSTE-ACS in a high-risk older patient group.

Clinical guidelines recommend a holistic, patient-centred approach when managing older adults with NSTE-ACS.[6 7] Given population ageing, there is an increasing need for clinicians to incorporate assessment of comorbidity into their decision-making and have adequate information when communicating the associated risks of adverse clinical outcomes with patients and their families. However, older, high-risk adults are under-represented in clinical research and, therefore, the evidence to guide decision-making is limited, which is reflected in the lack of specific guideline recommendations regarding patients with multimorbidity.[10]

In our study, patients with multimorbidity had a 62.5% increased risk of the primary composite outcome at 5 years compared with those without, which was primarily driven by an increased incidence of all-cause death. In this long-term follow-up, it is interesting to note that the Kaplan-Meier curves separate early between the groups. A truncated 1-year analysis finds a graphical separation of the curves at around day 200 postangiography, with a statistically significant difference in the composite primary outcome at 1 year. A full 1-year analysis of the ICON-1 cohort has been previously published.[22] These findings suggest that the impact of multimorbidity begins to have an impact on patient outcomes soon after invasive management of NSTE-ACS. Given that the patients in this study have been selected for an invasive rather than conservative approach by their treating clinician, our findings re-emphasise the importance of careful patient selection and risk–benefit decisions when considering the optimal approach for the oldest, most comorbid patients. Given these relatively early adverse outcomes, timely out-patient follow-up to ensure cardiovascular and non-cardiovascular comorbidities are appropriately managed may be prudent. This should include access to cardiac rehabilitation, particularly as older people are often relatively sedentary following ACS.[23 24] In an analysis of the Myocardial Ischaemia National Audit Project registry, optimal care for ACS in those with multimorbidity was associated with improved long-term survival, with the interesting exception of those with heart failure and cerebrovascular disease.[25] There is evidence that older patients with multimorbidity may cluster into different phenotypical groups depending on underlying conditions, with each multimorbidity phenotype having differing risk of cardiovascular disease, with the highest risk phenotypic cluster including heart failure, peripheral vascular disease and hypertension.[26] In our study, in the most multimorbid patients (CCI ≥6), 20% had concurrent heart failure, 28.8% had cerebrovascular disease and 79.8% had hypertension. The findings of this study lend weight to the argument that multimorbidity is a heterogeneous risk factor, and that more prospective data are needed to inform individualised care for the oldest patients presenting with NSTE-ACS.

The importance of the impact of cardiac interventions on health-related quality of life (HRQoL) is being increasingly recognised in this older population—but is often

Table 2 Clinical presentation, procedural and angiographic characteristics stratified by CCI score

	Total (n=264)	CCI 3 to 5 (n=160)	CCI ≥6 (n=104)	P value
Presentation and management strategy				
NSTEMI, n (%)	212 (80.3)	126 (78.8)	86 (82.7)	0.527
UA, n (%)	52 (19.7)	34 (21.3)	18 (17.3)	0.527
PCI, n (%)	220 (83.3)	137 (85.6)	83 (79.8)	0.239
CABG, n (%)	7 (2.7)	5 (3.1)	2 (1.9)	0.707
Medical management, n (%)	37 (14.0)	18 (11.3)	19 (18.3)	0.146
Procedural characteristics				
Arterial access, n (%)				
Right femoral artery	36 (13.6)	24 (15.0)	12 (11.5)	0.173
Right radial artery	224 (84.8)	134 (83.8)	90 (86.5)	
Left femoral artery	2 (0.8)	2 (1.3)	0 (0)	
Left radial artery	2 (0.8)	0 (0)	2 (1.9)	
One vessel PCI, n (%)	160 (60.6)	101 (63.1)	59 (56.7)	0.299
Multi-vessel PCI, n (%)	61 (23.1)	59 (36.9)	45 (43.3)	0.772
Lesion to receive PCI, n (%)				
Left main stem	17 (6.4)	5 (3.1)	12 (11.5)	**0.007**
Left anterior descending	127 (48.1)	82 (51.3)	45 (43.3)	0.205
Left circumflex	71 (26.9)	46 (28.7)	25 (24.0)	0.399
Right coronary artery	73 (27.7)	40 (25.0)	33 (31.7)	0.232
Saphenous vein graft	3 (1.1)	3 (1.9)	0 (0)	0.160
Number of stents	1(1)	1(1)	1(1)	n.s.
Type of stent, n (%)				0.429
Drug eluting stent	209 (79.2)	130 (81.3)	79 (76.0)	
Bare metal stent	5 (1.9)	3 (1.9)	2 (1.9)	
Duration of procedure, minutes	60.0(43)	60.0(41.0)	58.0(49.5)	0.304

Normally distributed continuous variables are reported as mean (±SD), non-normally distributed continuous variables are reported as median (IQR). Statistically significant results (p≤0.05) are displayed in bold.
CCI, Charlson comorbidity index; n.s., not significant; PCI, percutaneous coronary intervention.

reported to be poor by older adults following NSTE-ACS.[27] In a large national longitudinal cohort study, increasing comorbidity was associated with worsening HRQoL.[28] The large increase in the risk of death at 5 years that we show suggests that the primary focus in older adults with significant multimorbidity and NSTE-ACS should be on interventions that also provide benefits in quality of life. Given the paucity of existing evidence, there is need for randomised trials in older people with comorbidities to guide the most appropriate management strategies and allow honest, patient-centred discussions about the goals of management. The on-going British Heart

Table 3 Five-year outcomes stratified by CCI score

	Total (n=264)	CCI 3 to 5 (n=160)	CCI ≥6 (n=104)	P value
Primary composite outcome, n (%)	127 (48.1)	62 (38.8)	65 (62.5)	<0.001
Death	82 (31.0)	33 (20.6)	49 (47.1)	<0.001
Myocardial infarction	36 (13.6)	17 (10.6)	19 (18.3)	0.077
Repeat unplanned revascularisation	33 (12.5)	18 (11.3)	15 (14.4)	0.446
Stroke	10 (3.8)	9 (5.6)	1 (1.0)	0.052
Significant bleeding*	27 (10.2)	13 (8.1)	14 (13.5)	0.162

Statistically significant results (p<0.05) are displayed in bold.
*Significant bleeding is defined as Bleeding Academic Research Consortium (BARC) type 2 or greater.
CCI, Charlson comorbidity index.

Table 4 Univariate and multivariate Cox regression models for the association between CCI score and incidence of the primary composite outcome at 5 years

	Charlson Co-morbidity Index CCI≥6 vs CCI 3 to 5†	
Incidence of the primary composite outcome at 5 years*	**HR (95% CI)**	**P value**
Model 1—unadjusted	2.09 (1.47 to 2.96)	**<0.0001**
Model 2—adjusted for age and sex	1.67 (1.16 to 2.40)	**0.005**
Model 3—adjusted for age, sex and management strategy‡	1.64 (1.14 to 2.35)	**0.007**
Model 4—adjusted for age, sex, management strategy,‡ and GRACE 2.0 score	1.68 (1.14 to 2.47)	**0.009**

Statistically significant results (p<0.05) are displayed in bold.
*Primary outcome is composite death, myocardial infarction, stroke, unplanned repeat revascularisation or significant bleeding.
†CCI 3 to 5 used as reference.
‡Medical management versus PCI or CABG.
CABG, coronary artery bypass graft; CCI, Charlson co-morbidity index; PCI, percutaneous coronary intervention.

Foundation (BHF) SENIOR-RITA trial (NCT03052036) is a large (n=1600) randomised trial investigating the role of invasive management in all-comer older adults with NSTE-ACS and will collect data on multimorbidity.

There are some significant strengths to our study. Despite the well-described difficulties in recruiting older adults into clinical studies,[10] we describe a cohort of very old adults with a robust study design who were followed up prospectively for 5 years. Of 629 patients approached, 457 patients (72.7%) were eligible for inclusion and 300 were included in the ICON-1 cohort (47.7%). We have previously published an analysis of our screening log data;[10] however, in summary, the final population did not significantly differ from the population screened or eligible despite recruitment of fewer female patients (46% vs 39%, p=0.03) and mode of presentation (NSTEMI comprised 82% of the recruited cohort vs 76.1% of eligible patients, p<0.001). Risk factor distributions in screened, eligible and recruited populations were similar. Despite a modest sample size, a high event rate over 5 years allows meaningful conclusions to be made. Previous studies focusing on multimorbidity have recruited a younger patient cohort, with a shorter follow-up, or have been registry studies. However, we recognise the limitations of our work. The sample size precludes sub-group analysis, and the analysis of secondary outcomes is likely to be under-powered. More granular analysis of multimorbidity, in particular, the impact of phenotypic clusters

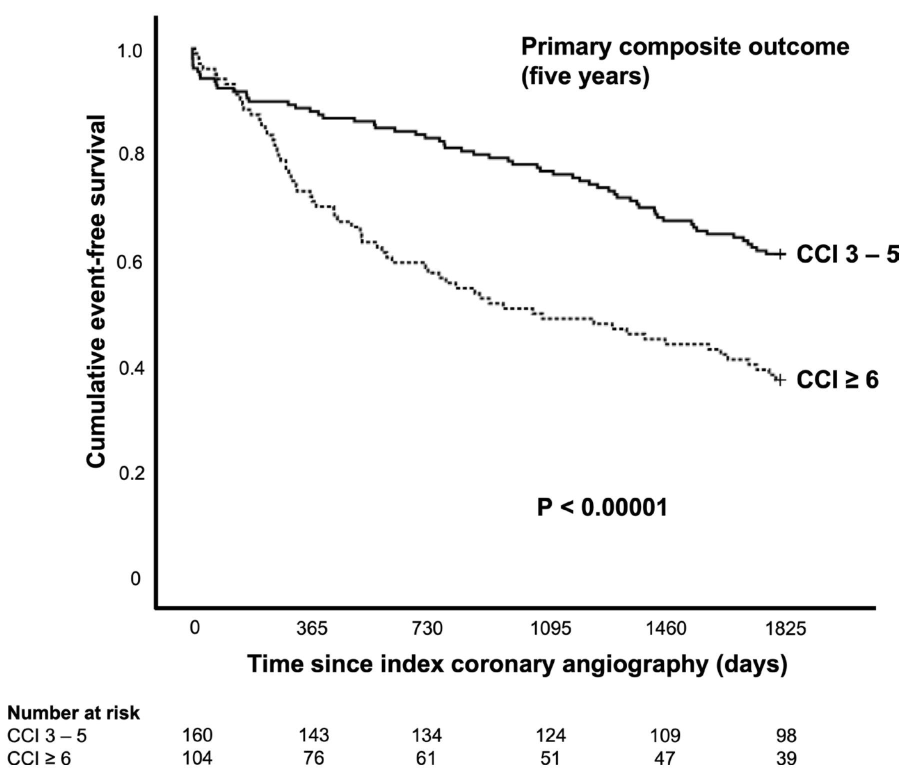

Figure 2 Cumulative event-free survival from the primary composite outcome at 5 years, stratified by CCI score. CCI, Charlson Co-morbidity Index score. P value from the Log-rank test.

of multimorbidity on outcomes, was not possible and should be examined in a future prospective cohort study. Nevertheless, the high rate of events, and, in particular, the 5-year mortality rate, is a novel and important finding. While we report all-cause rather than cardiovascular-specific mortality, this is relevant to real-world practice in this older population with multimorbidity. Given that all patients in the current study underwent coronary angiography, we do not capture patients treated with a conservative strategy. This group is being evaluated in the ongoing BHF SENIOR-RITA trial.

Conclusion

There is a high burden of multimorbidity in older adults referred for coronary angiography for NSTE-ACS. Increasing multimorbidity is associated with adverse long-term outcomes: on average, each additional CCI comorbidity was associated with a 31% increased adjusted risk of all-cause mortality at 5 years. Further studies on how to mitigate the impact of multimorbidity on clinical outcomes after NSTE-ACS in the very oldest adults are needed, so we can provide individualised, high-quality care for this rapidly expanding group of patients.

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Acknowledgements We are grateful to the patients that participated in this study, and to the Newcastle cardiovascular research team for their support with the long-term follow-up.

Contributors BB wrote the original manuscript, was involved in data collection, performed formal analysis and was involved in manuscript review and editing. GBM contributed to the original manuscript and was involved in data collection. HR was involved in manuscript review and editing. CW was involved in manuscript review and editing. AD contributed to manuscript review and editing. VK conceptualised the study and is responsible for the overall content as the guarantor, and was involved in supervision, project administration, funding acquisition and manuscript review and editing.

Funding This research is supported by the National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre based at Newcastle-upon-Tyne Hospitals NHS Foundation Trust and Newcastle University (no grant number). VK has received research funding from the British Heart Foundation (CS/15/7/31679). BB is funded by the NIHR as an Academic Clinical Fellow. CW is funded by the NIHR as an Academic Clinical Lecturer. AAD receives research funding from the Pepper Scholars Program of the Johns Hopkins University Claude D. Pepper Older Americans Independence Center funded by the National Institute on Aging P30-AG021334 and mentored patient-oriented research career development award from the National Heart, Lung, and Blood Institute K23-HL153771-01. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The extended 5-year follow-up underwent separate ethical approval in December 2020. The study was carried out in accordance with the Declaration of Helsinki. Informed, written consent was obtained from all participants by members of the research team. This study involves human participants and was approved by Newcastle regional ethics committee (12/NE/0160).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. At the time of patient recruitment, the authors did not obtain consent from patients to share data in the public domain. Given the study and follow-up are complete, the authors are not in a position to obtain consent from patients retrospectively to share the data in the public domain. Data are available on request to the Chief Investigator at vijay.kunadian@newcastle.ac.uk, and the Study Sponsor Newcastle Joint Research Office, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Level 1, Regent Point, Regent Farm Road, Gosforth, Newcastle Upon Tyne, NE3 3HD (Tel: 044 191 2824454) (trust.r&d@nuth.nhs.uk).

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