Title:

Comparison between first and second wave of COVID-19 outbreak in older people. The COPE multicentre European observational cohort study.

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Abstract

Background: Effective shielding measures and virus mutations have progressively modified the disease between the waves, likewise health care systems have adapted to the outbreak. Our aim was to compare clinical outcomes for older people with COVID-19 in Wave 1 (W1) and 2 (W2).

Methods: All data, including the Clinical Frailty Scale (CFS), were collected for COVID-19 consecutive patients, aged ≥65, from thirteen hospitals, in W1 (February-June 2020) and W2 (October 2020-March 2021). The primary outcome was mortality (time to mortality and 28-day mortality). Data were analysed with multilevel Cox proportional hazards, linear and logistic regression models, adjusted for wave baseline demographic and clinical characteristics.

Results: Data from 611 people admitted in W2 were added to and compared with data collected during W1 (N=1340). Patients admitted in W2 were of similar age, median [IQR], W2= 79 [73-84]; W1=80 [74-86]; had a greater proportion of men (59.4% *vs* 53.0%); had lower 28-day mortality (29.1% *vs* 40.0%), compared to W1. For combined W1-W2 sample, W2 was independently associated with improved survival: time-to-mortality aHR= 0.78 (95%CI 0.65-0.93), 28-day mortality aOR=0.80 (95%CI 0.62-1.03). W2 was associated with increased length of hospital stay aHR=0.69 (95%CI 0.59-0.81). Patients in W2 were less frail, CFS (adjusted mean difference [aMD]=-0.50, 95%CI -0.81, -0.18), as well as presented with lower CRP (aMD=-22.52, 95%CI -32.00, -13.04).

Conclusions: COVID-19 older adults in W2 were less likely to die than during W1. Patients presented to hospital during W2 were less frail and with lower disease severity and less likely to have renal decline.

Keywords: COVID-19; frailty; older patients; mortality rate; predictors of death.

Introduction

Since the novel coronavirus SARS-CoV-2 first appeared in late 2019, it has spread globally leading to 175 million confirmed cases, and around 3.79 million COVID-19 related deaths in the second week of June 2021.[1] Although the number of deaths represents only a small proportion of all infections, vulnerable older people represent a high percentage of the fatalities.[1-3]

While it has been a struggle to find a specific treatment, there have been definitely significant differences between the waves of the pandemic. With the rapid progression of the outbreak, national lockdowns, shielding measures, easier access to the swab test and active case detection have been required in order to reduce the viral transmission and number of cases. As a result, the number of people in hospital with COVID-19 has been gradually declining after the first wave. The national health care systems have been organized according to the COVID-related burden with hospital ward adaptation. In addition, therapies such as respiratory support [4] and systemic corticosteroids [5] have improved the COVID-19 management and contributed to better clinical outcomes in hospitalized patients. However, the access to these therapies for older adults is less certain.

Considering all these factors, there is little evidence comparing the first to the second wave and focusing on the outcomes in older people when hospitalized for COVID-19.

The COPE (**C**OVID-19 in **O**lder **Pe**ople) study [6] assessed outcomes in patients hospitalized with COVID-19, with a particular focus on older adults living with frailty. We demonstrated that pre-admission frailty, measured using the Clinical Frailty Scale, was associated with both mortality and length of hospital stay independent of age.[7]

During the autumn of 2020, the second wave of the pandemic began in Europe. The COPE study team [6,7] set up the COPE 1.1 study. Research comparing outcomes between different

waves is limited to retrospective analyses, including mainly younger patients, those admitted to intensive care units, or analysed using underpowered samples.[8-10]

The COPE 1.1 is a multicentre prospective cohort study providing real world data from people admitted to hospital with COVID-19. We aimed to compare clinical and demographic features of older adults and identify differences in outcomes between the two waves of the pandemic, specifically mortality and length of stay.

Methods

Study design

We conducted a prospective cohort study, full study details can be found within the COPE protocol.[6] The data of the second cohort of patients were gathered between 1st October 2020 and 8th March 2021 as an extension of the COPE study [7] during the second wave of the COVID-19 pandemic in the UK and Italy.

Authority in the UK to conduct the study was granted by the Health Research Authority (20/HRA/1898), and in Italy by the Ethics Committee of Hospital Policlinico Modena (Reference 369/2020/OSS/AOUMO). This manuscript follows the STROBE statement for reporting of cohort studies.[11]

Setting

We utilised the same network of clinical teams from twelve UK sites and one Italian site (www.opsoc.eu) that participated in the COPE study.[6,7]

The UK hospitals that participated in data collection are: Aberdeen Royal Infirmary, Glasgow Royal Infirmary, Inverclyde Royal Hospital, Maidstone Hospital, Nevill Hall Hospital in Abergavenny, Royal Alexandra Hospital in Paisley, Royal Gwent Hospital in Newport, Southmead Hospital in Bristol, Salford Royal Hospital, University Hospital of Wales in Cardiff, Ysbyty Gwynedd in Bangor, and Ysbyty Ystrad Fawr in Caerphilly. The Italian centre is the University Hospital Policlinico in Modena.

Participants

Consecutive patients admitted to hospital between 27th February and 10th June 2020 (Wave 1), and between 1st October 2020 and 8th March 2021 (Wave 2), aged 65 years or older with a

diagnosis of COVID-19 were included. Patients with ≥65 years hospitalized for other reason who acquired SARS-CoV-2 infection in hospital were also included. Diagnostic criteria were laboratory confirmed SARS-CoV-2 positive swabs, and a clinical diagnosis (made by the site clinical team and based on signs, symptoms and/or radiology) consistent with COVID-19. No exclusion criteria were applied. Data regarding demographics and comorbidities were systematically collected on admission. The diagnosis of a comorbidity was confirmed by patient's medication list or medical record. Clinical teams at each site screened inpatient admission lists for eligibility.

Sample size Justification

Prior to this study mortality was known during wave 1 of 40%, and it was estimated to be 30% in wave 2 (Hazard Ratio [HR] of 0.70). In order to detect this difference with 90% power and 5% significance 1.000 participants would be needed, with at least 500 during wave 2.

Variables and outcomes

Covariates collated included: age; sex; admission C-reactive protein as a marker of disease severity (CRP, ≥40 mg/dL); [12] admission estimated glomerular filtration rate (eGFR, <60 ml/min/1.73m^2); smoking status (never, previous, or current); frailty, and current diagnosis of: hypertension, coronary artery disease (CAD), and diabetes mellitus. Dexamethasone usage and remdesivir (wave 2 only). Frailty was measured by the researcher using the Clinical Frailty Scale (CFS 1-9)[13,14] estimated two weeks prior to admission.

The primary outcome was in-hospital mortality (time to mortality and 28-day mortality). The secondary outcome were: 1) characteristics differences in patient cohorts between the two waves; 2) length of hospital stay (time from admission to discharge); 3) potential predictors

of death. Outcomes were assessed up to last data entry using systems of prospective follow-up and electronic health records.

Data Analysis

Data from Wave 1 and Wave 2 were compared in terms of baseline demographic and clinical variables and outcomes.

Main Outcomes: Time-to-event outcomes (mortality, and time to discharge) were analysed using multilevel multivariable Cox proportional hazards (PH) regression models, and Day 28 Mortality was analysed with a multilevel logistic regression.

Each Cox PH model fitted site as a random effect to account for heterogeneity between each hospital. Crude and adjusted Hazard Ratios (HR) are presented with associated 95% Confidence Intervals (CI). Day 28 mortality was analysed using multilevel logistic regression models fitting hospital as a random intercept effect, estimating crude and adjusted Odds Ratios (OR) with associated 95% CIs. All models were adjusted for Wave (1 or 2), healthcare setting (Italy or UK), age (65-74; 75-84; 85-94; 95+), sex (female/male), smoking status (current, former, never), elevated CRP (≥40 mg/dL), diabetes (yes/no), CAD (yes/no), hypertension (no, yes, yes and on treatment), reduced renal function (<60 mL/min per 1.73 m^2), and frailty (CFS 1-3; CFS 4; CFS 5-6; CFS 7-8). Due to the small number of patients with a terminal illness (CFS 9), these were excluded from the analyses. The sample size calculation was originally estimated in the COPE protocol.[6] Time-to-event models were visualised using Kaplan-Meier survival curves. Analyses were carried out in Stata SE version 16. Kaplan-Meier plots were visualised in R.

Secondary analysis of the participant characteristics between wave 1 *vs* 2.

To assess if mortality differed by wave due to participant characteristics we examined the difference between the first and second wave. Fitting each participant characteristic as the dependent variable the crude and adjusted effect of wave was estimated using mixed-effects linear regression models (for age, CRP, eGFR and CFS), and mixed effects logistic regressions (for healthcare [UK *vs* Italy], sex, smoking [current *vs* never/ex-smokers], hypertension, diabetes, and CAD). All models were fitted with a random effect to account for hospital. All multivariable analyses were adjusted using the same covariates from the main outcome analyses.

Results

The study involved a total of 1951 patients aged 65 years and over (Wave 1, N=1340; Wave 2, N=611). People admitted during the second wave were of a similar age; median (IQR) age in Wave 1 was 80 (74-86) and 79 (73-84) in Wave 2. 710 (53.0%) patients in Wave 1 were male, compared to 363 (59.4%) in Wave 2 (**Table 1**). There were 1722 (88.3%) patients included from the UK (1251 in Wave 1 and 471 in Wave 2) and 229 (11.7%) from Italy (89 in Wave 1 and 140 in Wave 2). People admitted to hospital in Wave 2 were less likely to be living with frailty. In Wave 1, 66.5% of patients (N=892) were frail (CFS 5 and greater), compared to 51.4% (N=314) in Wave 2 (**Table 1**). Fifty-five cases of missing smoking status were imputed as never smokers. Similarly, 64 cases of missing eGFR were imputed as normal (≥60 ml/min/1.73m^2). In Wave 1, only 23 (1.7%) of patients were taking dexamethasone compared to 339 (55.5%) in Wave 2. Remdesivir data were not collected in Wave 1, 87 (14.2%) of patients received it in the second wave. The prevalence of comorbidities was similar in the two waves. Disease severity assessed by elevated CRP appeared lower during Wave 2 (CRP ≥40, 59.7% *vs* 68.8%) (**Table 1, eTable 1**). None of the patients included in Wave 2 were admitted in Wave 1.

Primary outcome (Time to mortality, and Day 28 Mortality)

The 28-day mortality rate in Wave 1 was 40.0% (N=536), and 29.1% (N=178) in Wave 2. Median (IQR) time from admission to mortality was 12 (6-25) days in Wave 1 and 22 (11-50) days in Wave 2 (**Table 1**, **Figure 1**). In the multivariable analysis, Wave 2 was independently associated with reduced mortality (aHR 0.78, 95%CI 0.65-0.93) (**Table 3**). In addition, crude analysis revealed that older age, increasing frailty, male sex, elevated CRP, and reduced renal function were associated with increased mortality (**Table 3**).

Similar associations were found for 28-day mortality. Wave 2 was marginally associated with reduced mortality (aOR 0.80, 95%CI 0.62-1.03) (**eTable 4 in the Supplemental File**). Older age, living with frailty, being male, increased CRP and decreased renal function were associated with increased mortality (**eTable 4 in the Supplemental File**).

Secondary Outcome (Time to discharge)

Wave 2 was associated with a longer length of hospital stay (aHR 0.69, 95%CI 0.59-0.81) (**eTable 5 in the Supplemental File**). Additionally, increasing frailty (compared to CFS 1-3: CFS 5-6, aHR 0.78, 95%CI 0.65-0.94; CFS 7-8, aHR 0.76, 95%CI 0.61-0.94), and age (85-94 compared to 65-74, aHR 0.76, 95%CI 0.62-0.94) were associated with longer length of stay.

Secondary analysis of the participant characteristics between Wave 1 vs 2

Additional analyses suggested that patients in Wave 2 were less frail (adjusted Mean Difference, aMD = -0.50, 95%CI -0.81, -0.18), and presented with a reduced disease severity expressed by lower CRP (aMD = -22.52, 95%CI -32.00, -13.04). There was no difference found in age between Wave 1 and 2 (**eTable 1 in the Supplemental File**).

Discussion

We included 1951 participants in this study and found that the mortality rate for hospitalised older patients was lower in the second wave, when compared to the first wave of COVID-19. Our data also showed that people admitted to hospital during the second wave were noticeably less frail and presented with a lower disease severity as expressed by lower CRP.

An enlarging evidence base and increasing experience from frontline clinicians should have improved patient management since the first wave of the pandemic. Our findings demonstrated a reduction in hospital mortality during the second wave that can be explained by healthier patients being admitted who were less frail and had lower disease severity. It is likely that a better use of respiratory support (high flow nasal cannula oxygen therapy and non-invasive ventilation) and critical care [4] may have partially contributed to the better outcomes we found.

Additionally, since the first wave, there has been an increase in the use of systemic corticosteroids in COVID-19 patients[5]. In the second wave 55% of participants were taking dexamethasone, compared to 1.7% and 15% of our participants were taking remdesivir. Further, it is possible that other factors such as severity of infection (viral load and virus variants) and host response [15] may have contributed to the reduced mortality in our population. There is some evidence confirming that in-hospital mortality from COVID-19 declined after the first wave. As an example, a prospective study of hospitalized patients of all ages in Spain found that mortality rate decreased in the second wave of outbreak with less patients treated with intubation.[9] Finally, it is also possible that easier access to testing for SARS-CoV-2 along with advice about seeking medical help might have resulted in earlier presentation to hospital, resulting in earlier treatments.[16]

We also found that the time until hospital discharge was longer during the second wave, compared to the first. There are several potential reasons for this. Firstly, increased survival will result in more people being discharged from hospital, some of which may have stayed for a longer period of time. Hospital care was also more organised and prepared for the second wave, leading to a lower pressure on hospital beds and the urgent need for discharge. Further to this, all hospital patients, including those requiring external help at home, were required to test negative for COVID-19, to prevent onwards transmission and people living in residential care facilities were not able to be discharged if there was an ongoing outbreak at their care facility.

We found that the prevalence of frailty in our population aged over 65 years was 51.4%, markedly lower than we previously reported in the original COPE-Wave 1 study (66.9%).[7,17] Frailty is known to contribute to mortality in COVID-19.[7,18,19] Therefore it is not surprising that the mortality rate in the second wave was lower. As the pandemic has progressed, awareness of the impact of the disease severity in people living with frailty has increased.[20,21] SARS-CoV-2 infection has been under-diagnosed at the beginning and COVID-19 outbreaks have been common and severe in long term care facilities.[22] It is therefore possible that many older people living with frailty and with diagnosis of COVID-19 died in the first wave or were not admitted to hospital and remained in their place of residence in the second wave. This fact is highlighted by the numbers of people admitted with CFS of 7-8 between the two waves (28.1% *vs* 14.2%).

While community-based care of people with COVID-19 has increased and improved since the first wave, our study demonstrates a reduction in admission in the group of frail people, who are known to be susceptible to COVID-19.

We previously demonstrated that a raised CRP can predict mortality, supporting the role of this acute-phase protein as a prognostic marker in COVID-19.[12,23,24] We also found that levels of CRP were lower in Wave 2 than Wave 1 which is indicative of lower disease severity of the viral disease showing a lower inflammatory response in Wave 2. We also observed a reduced renal decline in Wave 2. Acute deterioration in chronic kidney disease due to systemic infection by COVID-19 as potential underlying trigger has been frequently observed at hospital presentation.[25,26]

Our findings should be interpreted in the light of a number of limitations. First, data for our Wave 2 study were collected from a subset of hospitals in the Wave 1 study.[7] Second, we only included patients who were admitted to hospital and we only analysed mortality during hospital stay. This has implications in assessing the overall mortality rate for COVID-19 and the need to ensure that both inpatient and community mortality are considered. Moreover, the study also did not include patients who died in emergency departments (before hospital admission). In addition, although none of the patients included in Wave 2 were admitted in Wave 1, it is unknown if they have been previously infected from SARS-CoV-2. Given the enrolment dates in both countries, it is unlikely they were vaccinated before admission to hospital in the second wave.

This study has several clinical implications which impact on public health and future research. First, the study provided real-world data from large cohort of older patients with COVID-19 in hospital settings in UK and Italy, this adds value to the wider generalisability of the study findings. The population during the second wave was representative of other cohorts, as demonstrated by the demographic data and prevalence of comorbidities that are in line with other studies and comparable to other COVID populations.[9,20,21]

Second, the study highlights the importance of assessing the level of frailty in patients presented to emergency departments with suspected SARS-CoV-2 infection, confirming that frailty has important implications for therapy and prognosis. Chronological age may not be sufficient for describing the concept of wider vulnerability in older populations. Future research might explore the relationship between the degree of pre-admission frailty and care such as use of mechanical ventilation (intubation) and systemic corticosteroids in older patients.

Third, our study reported a reduced proportion of frail people admitted to hospital, however patients living with frailty should continue to present to hospital for care and should be investigated and offered the best available care for COVID-19. Further, it is essential to look for differences between outcomes of COVID-19 between primary and secondary care to ensure the people living with frailty are being managed in the correct health care setting.

Conclusions

This study demonstrated a lower mortality rate between the first two waves of the COVID-19 pandemic. The population in the second wave was significantly less frail, and presented with a lower disease severity.

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Conflict of interests

We declare no competing interests.

Key points

- Real world data on the comparison of COVID-19 in-hospital mortality in older adults between Wave 1 and Wave 2 of the pandemic were analyzed.
- The Clinical Frailty Scale was used for a clinical assessment of frailty.
- A reduced COVID-19 in-hospital mortality in older adults was demonstrated and a less frail population admitted to hospital was reported in Wave 2.
- This evidence supports that patients living with frailty need to be treated with the same level of investigation as non frail patients and further research on the mortality rate within this population should be precisely estimated.
- These findings confirm that frailty has important implications for COVID-19 management and prognosis.

Acknowledgments

Contributions of authors

All authors contributed to the interpretation of results and in making an important intellectual contribution to the manuscript. All authors read and approved the final manuscript.

JH conceived the concept of the study. BC managed the project, AV did the literature review. BC and RS did data analysis and interpreted the findings and RS did statistical analysis and graphics. AV, BC, JH, RS wrote the first draft of the manuscript. All authors approved the final manuscript.

JH is the guarantor of the study.

Data sharing and data availability

All data sharing and collaboration requests should be directed to the corresponding author. The data underlying this article are available in the article and in its online supplementary material.

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Tables and Figures

Tables

Table 1: Sample characteristics by wave

		Wave 1 (N=1,340)	Wave 2 (N=611)	Total (N=1,951)
		N (%)	N (%)	N (%)
28-day Mortality				
	Alive	737 (55.0)	425 (69.6)	1162 (59.6)
	Dead	536 (40.0)	178 (29.1)	714 (36.6)
	Missing	81	8	89
Healthcare				
	Healthcare	1251 (93.4)	471 (77.1)	1722 (88.3)
	UK	89 (6.6)	140 (22.9)	229 (11.7)
Age				
	65-74	378 (28.2)	180 (29.5)	558 (28.6)
	75-84	539 (40.2)	285 (46.6)	824 (42.2)
	85-94	384 (28.7)	135 (22.1)	519 (26.6)
	95+	39 (2.9)	11 (1.8)	50 (2.6)
Sex				
	Female	629 (46.9)	248 (40.6)	877 (45.0)
	Male	710 (53.0)	363 (59.4)	1073 (55.0)
	Missing	1	0	1
Smoking				
	Never Smokers	645 (48.1)	264 (43.2)	909 (46.6)
	Ex-smokers	568 (42.4)	304 (49.8)	872 (44.7)
	Current Smokers	76 (5.7)	39 (6.4)	115 (5.9)
	Missing	51	4	55
Diabetes				
	No	952 (71.0)	432 (70.7)	1384 (70.9)
	Yes	384 (28.7)	179 (29.3)	563 (28.9)
	Missing	4	0	4
Hypertension				
	No	588 (43.9)	260 (42.6)	848 (43.5)
	Yes	200 (14.9)	136 (22.3)	336 (17.2)
	Yes and on treatment	552 (41.2)	215 (35.2)	767 (39.3)

CAD				
	No	982 (73.3)	455 (74.5)	1437 (73.7)
	Yes	355 (26.5)	155 (25.4)	510 (26.1)
	Missing	3	1	4
CRP				
	<40	418 (31.2)	246 (40.3)	664 (34.0)
	≥40	922 (68.8)	365 (59.7)	1287 (66.0)
eGFR				
	≥60	707 (52.8)	321 (52.5)	1028 (52.7)
	<60	575 (42.9)	284 (46.5)	859 (44.0)
	Missing	58	6	64
CFS				
	CFS 1-3	256 (19.1)	164 (26.8)	420 (21.5)
	CFS 4	172 (12.8)	131 (21.4)	303 (15.5)
	CFS 5-6	487 (36.3)	224 (36.7)	711 (36.4)
	CFS 7-8	377 (28.1)	87 (14.2)	464 (23.8)
	CFS 9	28 (2.1)	3 (0.5)	31 (1.6)
	Missing	20	2	22

Excluded* due to being alive and in hospital with less than 28 days of follow-up.

Table 2: Sample characteristics by in-hospital mortality

		Alive (N=1141)	Dead (N=810)	Total (N=1951)
		N (%)	N (%)	N (%)
Healthcare				
	UK	1011 (58.7)	711 (41.3)	1722 (88.3)
	Italy	130 (56.8)	99 (43.2)	229 (11.7)
Wave				
	1	760 (56.7)	580 (43.3)	1340 (68.7)
	2	381 (62.4)	230 (37.6)	611 (31.3)
Age				
	65-74	378 (67.7)	180 (32.3)	558 (28.6)
	75-84	472 (57.3)	352 (42.7)	824 (42.2)
	85-94	268 (51.6)	251 (48.4)	519 (26.6)
	95+	23 (46.0)	27 (54.0)	50 (2.6)
Sex				
	Female	544 (62.0)	333 (38.0)	877 (45.0)
	Male	596 (55.5)	477 (44.5)	1073 (55.0)
	Missing	1	0	1
Smoking				
	Never Smokers	549 (60.4)	360 (39.6)	909 (46.6)
	Ex-smokers	485 (55.6)	387 (44.4)	872 (44.7)
	Current Smokers	73 (63.5)	42 (36.5)	115 (5.9)
	Missing	34	21	55
Diabetes				
	No	821 (59.3)	563 (40.7)	1384 (70.9)
	Yes	318 (56.5)	245 (43.5)	563 (28.9)
	Missing	2	2	4
Hypertension				
	No	492 (58.0)	356 (42.0)	848 (43.5)
	Yes	200 (59.5)	136 (40.5)	336 (17.2)
	Yes and on treatment	449 (58.5)	318 (41.5)	767 (39.3)
CAD				
	No	861 (59.9)	576 (40.1)	1437 (73.7)
	Yes	279 (54.7)	231 (45.3)	510 (26.1)

	Missing	1	3	4
CRP				
	<40	460 (69.3)	204 (30.7)	664 (34.0)
	≥40	681 (52.9)	606 (47.1)	1287 (66.0)
eGFR				
	≥60	650 (63.2)	378 (36.8)	1028 (52.7)
	<60	452 (52.6)	407 (47.4)	859 (44.0)
	Missing	39	25	64
CFS				
	CFS 1-3	299 (71.2)	121 (28.8)	420 (21.5)
	CFS 4	183 (60.4)	120 (39.6)	303 (15.5)
	CFS 5-6	411 (57.8)	300 (42.2)	711 (36.4)
	CFS 7-8	223 (48.1)	241 (51.9)	464 (23.8)
	CFS 9	9 (29.0)	22 (71.0)	31 (1.6)
	Missing	16	6	22

Table 3: Cox-regression, time to mortality

	HR (95%CI)	p	aHR	P
Italy	0.64 (0.23-1.81)	0.405	0.85 (0.32-2.23)	0.740
Wave 2	0.75 (0.63-0.90)	0.001	0.78 (0.65-0.93)	0.007
Age (65-74)	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
75-84	1.47 (1.22-1.78)	p<0.001	1.38 (1.14-1.68)	0.001
85-94	1.70 (1.39-2.09)	p<0.001	1.51 (1.21-1.88)	p<0.001
95 & over	2.41 (1.58-3.68)	p<0.001	2.30 (1.49-3.56)	p<0.001
Male	1.12 (0.97-1.30)	0.119	1.20 (1.03-1.39)	0.022
Smoking (never)	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
Ex-smoker	1.22 (1.06-1.42)	0.008	1.14 (0.98-1.33)	0.086
Current smoker	0.96 (0.69-1.35)	0.832	0.95 (0.67-1.34)	0.766
CRP ≥40	1.84 (1.56-2.17)	p<0.001	1.82 (1.54-2.15)	p<0.001
Diabetes	1.08 (0.92-1.26)	0.353	1.03 (0.87-1.21)	0.749
CAD	1.13 (0.96-1.33)	0.136	1.02 (0.86-1.21)	0.797
Hypertension (no)	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
Yes	0.95 (0.78-1.17)	0.660	0.96 (0.78-1.19)	0.726
On treatment	0.90 (0.76-1.05)	0.182	0.89 (0.75-1.05)	0.167
eGFR <60	1.41 (1.22-1.62)	p<0.001	1.30 (1.12-1.50)	p<0.001
CFS 1-3	1.00 (1.00-1.00)		1.00 (1.00-1.00)	
CFS 4	1.36 (1.06-1.76)	0.018	1.26 (0.97-1.64)	0.079
CFS 5-6	1.49 (1.20-1.86)	p<0.001	1.34 (1.06-1.69)	0.015
CFS 7-8	2.01 (1.60-2.54)	p<0.001	1.78 (1.39-2.27)	p<0.001

Note: aHR adjusted for healthcare, wave, age, sex, smoking status, CRP, diabetes, CAD, hypertension, eGFR and CFS.