Nosocomial COVID-19 infection: examining the risk of mortality. The COPE-Nosocomial study (COVID in Older PEople).

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Manuscript word count:	2998
Abstract word count:	256
Number of Figures:	2
Number of Tables:	3
Number of Supplementary Tables	1
Number of Supplementary Figures	1

Abstract

Introduction

Hospital admissions for non-COVID-19 pathology have significantly reduced. It is believed that this may be due to public anxiety about acquiring COVID-19 infection in hospital and the subsequent risk of mortality. There is an urgent need for clarity regarding patients who acquire COVID-19 in hospital (nosocomial COVID-19 infection [NC]), their risk of mortality, compared to those with community acquired COVID-19 (CAC) infection.

Methods

The COPE-Nosocomial Study was an observational cohort study. The primary outcome was the time to all-cause mortality (estimated with an adjusted hazards ratio [aHR]), and secondary outcomes were Day-7 mortality and the time-to-discharge. A mixed-effects multivariable Cox's proportional hazards model was used, adjusted for demographics and comorbidities.

Results

Our study included 1564 patients from 10 hospital sites throughout the UK, and one in Italy, and collected outcomes on patients admitted up to 28th April, 2020. 12.5% of COVID-19 infections were acquired in hospital. 425 (27.2%) patients with COVID died. The median survival time in NC patients was 14 days, which compared to 10 days in CAC patients. In the primary analysis, NC infection was associated with reduced mortality (aHR=0.71, 95%CI 0.51-0.99). Secondary outcomes found no difference in Day-7 mortality (aOR=0.79, 95%CI 0.47-1.31), but NC patients required longer time in hospital during convalescence (aHR=0.49, 95%CI 0.37-0.66).

Conclusion

The minority of COVID-19 cases were the result of NC transmission. Whilst no COVID-19 infection comes without risk, patients with NC had a reduced risk of mortality compared to CAC infection, however, caution should be taken when interpreting this finding.

In the United Kingdom, authority to conduct the study was granted by the Health Research Authority (20/HRA/1898), and in Italy by the Ethics Committee of Policlinico Hospital Modena (Reference 369/2020/OSS/AOUMO). Cardiff University was the study sponsor.

Keywords

COVID-19; Nosocomial infection; community acquired infection

Introduction

The novel coronavirus SARS-CoV-2 is implicated in causing the disease COVID-19 and its associated complications. While most infected people develop mild flu-like symptoms, some have significant respiratory complications and go on to develop multiorgan failure (1) and death (2). Despite robust infection control efforts, hospital-acquired (herein described as nosocomial) COVID-19 infection have been reported (3 - 5). Heightened anxiety amongst the general public has resulted in individuals' reluctance to attend hospital for diagnostic tests or treatments. This may account for the significant reduction in acute hospital attendances (6) and possibly contributed to the high excess mortality toll.

The hallmark of SARS-CoV-2 is its highly contagious nature; it remains viable and infectious on surfaces for up to three days (7). Its main mode of transmission is through droplets and close contact with people with the disease (8). Incubation is estimated at 5-7 days (WHO), but this can take up to 14 days (9). Nosocomial infection is defined as an infection that is acquired in hospital by a patient who was admitted for a reason other than that infection (at least 15 days prior to a positive COVID-19 diagnosis), and in whom the pathogen was not incubating at the time of admission. Risk factors for developing a nosocomial infection include; age >70 years, immunosuppression, admission to intensive care, history of trauma, antibiotic use and use of an indwelling catheter (10). Prior to the current COVID-19 pandemic, nosocomial infections (most commonly from respiratory and urinary tracts and surgical wounds) already posed significant healthcare and economic burdens in both developed and resource-poor countries, with an average estimated prevalence of 8.7% worldwide (11).

In general, nosocomial infections are not life threatening. However, a large study in the United States reported that non-ventilator associated nosocomial pneumonia occurred in 2.1% of all hospital admissions, with a mortality rate of 13.1% (12). In addition, patients diagnosed with a nosocomial infection are likely to spend 2.5 times longer in hospital (13). SARS (Severe Acute Respiratory Syndrome, 2003) and the MERS (Middle East Respiratory Syndrome, 2012) had estimated nosocomial infection prevalence of 36% and 56% respectively (14). In comparison, Chinese estimates of the prevalence of nosocomial COVID-19 are as high as 41% (15-17). There is no current published data for nosocomial versus community acquired COVID-19 in UK hospitals, leaving uncertainty around morbidity or mortality and heightened public anxiety. A robust evidence base will help direct policy-makers and aid the dissemination of public health advice.

The COPE (**C**OVID-19 in **O**lder **Pe**ople study) study was designed to assess a number of clinical parameters and biomarkers as prognostic tools for patients with COVID-19. The aim of this secondary study was to assess the burden of nosocomial COVID-19 (NC) infection and determine

if patients with NC exhibited poorer outcomes to those who experienced community acquired COVID-19 (CAC) infection.

Methods

Study Design

Data were obtained as part of a multi-centre international cohort study: the COPE study (**C**OVID-19 in **O**lder **Pe**ople study), which assessed clinical and biomarkers as prognostic indicators of mortality. In the United Kingdom, authority to conduct the study was granted by the Health Research Authority (20/HRA/1898), and in Italy by the Ethics Committee of Policlinico Hospital Modena (Reference 369/2020/OSS/AOUMO). Cardiff University was the study sponsor. This manuscript follows the STROBE statement for reporting of cohort studies (18). Investigators at each site collated electronic and manual patient records. Prior to participating, all study personnel completed specific data collection training. Local policies on data protection were followed in order to record data securely at each site. Full study details can be found within the COPE protocol (19).

Setting

We utilised an established network of clinical teams with an interest in frailty from ten UK sites and one Italian site (www.opsoc.eu). The UK centres were Ysbyty Ystrad Fawr in Caerphilly, Royal Gwent Hospital in Newport, Nevill Hall Hospital in Abergavenny, University Hospital of Wales in Cardiff, Southmead Hospital in Bristol, Aberdeen Royal Infirmary, Royal Alexandra Hospital in Paisley, Inverclyde Royal Hospital, Salford Royal Hospital, and Glasgow Royal Infirmary. The Italian centre was the University Hospital of Modena Policlinico in Italy. All hospitals adhered to infection control guidelines with the application of appropriate personal protective equipment, isolation of suspected and confirmed cases, and had a policy of having no outside visitors during the period of data collection (20). All hospitals deliver urgent and emergency care to patients diagnosed with COVID-19. Data were collected from patients admitted with CVID from 27th February and 28th of April 2020. Further details of the study design are found within the protocol (19), and the main study findings are reported in the COPE study report (21). In the original protocol we estimated a 30% mortality in the frail, and 20% in those not frail (hazard ratio [HR] of 0·60). In order to detect this difference with 80% power and with a 5% significance, at least 500 patients were to be included. The sample size was increased to assess CFS categorised into four groups (rather than frail vs not frail) (19).

Participants

We attempted to include all consecutive patients admitted to hospital aged 18 years or older with a diagnosis of COVID-19. Diagnostic criteria were swabs confirming the presence of SARS-CoV-2, or a clinical diagnosis (made by the site clinical team and based on signs, symptoms and/or radiology) consistent with COVID-19. Patients were screened and excluded due to: not having a clinical (or laboratory) diagnosis; clinical documentation not available; or no available clinical resource for data capture. Clinical teams at each site screened in-patient admission lists for eligibility and had access to infection control records of positive COVID-19 laboratory testing. Screening logs of eligible participants were retained at each site.

Outcomes: The primary outcome was the time-to-mortality from the date of admission (or date of diagnosis, if diagnosis was five or more days after admission). For example, all 196 NC patients were diagnosed 15 or more days after admission, and were analysed as the time from diagnosis to outcome (death or discharge). The 169 CAC were analysed from the date of diagnosis to outcome (since they had a positive diagnosis between five and 14 days after admission could not be confirmed as true NC), with the remaining 1199 CAC analysed as the difference from admission to outcome. The time to event was censored at death or discharge.

Secondary outcomes: Day-7 mortality and the time-to-discharge (herein described as the length of stay).

We collected variables with prognostic utility (1, 22-24) which included: patient age sex; C-reactive protein (CRP) on admission (; estimated glomerular filtration rate (eGFR) on admission; smoking status (never, previous, or current); frailty; and previous or current history of: coronary artery disease, diabetes mellitus, and hypertension. Frailty was measured using the pre-admission Clinical Frailty Score (CFS) representing a patients' frailty two weeks prior to admission. The CFS is widely used within the UK to aid clinical management. The CFS is used as an ordinal hierarchical scale that numerically ranks frailty from 1 to 9, with a score of 1 being very fit, 2 well, 3 managing well, 4 vulnerable, 5 mildly frail, 6 moderately frail, 7 severely frail, 8 very severely frail and 9 terminally ill. For the purposes of the analyses scores were grouped into a clinically meaningful groups: 1-2, 3-4, 5-6 and 7-9 (25).

Data Analysis

Baseline demographic and clinical characteristics were partitioned by mortality, and location of infection to describe the included participants.

Time to mortality (primary outcome) and length of stay (secondary outcome) were analysed with mixed-effects multivariable Cox's proportional baseline hazards regression models. The analyses were fitted with a random effect to account for hospital variation (26), and adjusted for the base model of: patient age group; sex; smoking status; CRP; diabetes; hypertension ; coronary artery

disease; and the CFS. The adjusted hazard ratios (aHR) were estimated with associated 95% confidence intervals (95%CI). The baseline proportionality assumption was tested visually with log-log residuals. Each time to event analysis was reported with a Kaplan Meier survival plot.
The secondary outcome of Day-7 was analysed using a mixed-effects multivariable logistic model, fitting each hospital as a random intercept effect, and adjusted with covariates consistent with the primary outcome. The adjusted odds ratio (aOR) were estimated and presented with associated 95%CI. Missing data were explored for patterns of missingness. The primary outcome analysis was repeated within each of the co-morbidity subgroups to assess the impact of NC within each subgroup. Analysis was carried out using Stata version 15 (27). Kaplan Meier survival plots were generated in R (28).

Results

The COPE study screened 1,687 participants from general medical, surgical, geriatric, respiratory, and infectious diseases wards, as well as intensive care units where applicable. These wards solely managed suspected or confirmed COVID-19 patients. 143 patients were excluded from the study after screening, with the remaining 1,564 participants included. There were 1410 (90.2%) patients from the UK, and 154 (9.8%) from Italy (Table 1). Most were diagnosed laboratory testing (95.1%) and 64 (4.9%) by clinical diagnosis. Data quality was high and a complete case dataset was obtained for over 97% of included patients. There were 25 cases of missing smoking status, which were imputed as never smokers, and 32 cases of missing CRP, which were median imputed. Other missing covariates occurred in no more than 14 patients. Given the minimal degree of missing data, the complete case population was used within each analysis, and the number included shown as the population under investigation.

Descriptive data

The median patient age was 74 years old (IQR, 61-83), and 903 were male (57.7%). The overall in-hospital COVID-19 mortality rate was 27.2% (425/1564), and this varied throughout the 11 hospitals between 12.2% and 43.9%. Of all hospital episodes of COVID-19 infection, we found 12.5% were NC (196/1564) and 87.5% were CAC (1368/1564). The median proportion of NC infections from the total number of COVID-19 cases from the 11 hospitals was 8.7% (IQR, 3.0-14.1%). The median number of days between patient admission and a positive COVID-19 test for NC infection was 32.5 days (IQR, 23-54 days), and for CAC the median was 0 days (IQR, 0-1 days). The median patient age for NC infection was 80 years old (IQR, 71.5-86.5 years), and was 73 years old (IQR, 60-82 years) for patients with CAC infection (Supplementary Table 1). The median level of frailty was moderately frail [CFS=6] for NC, and vulnerable [CFS=4] for CAC. Full patient's demographics and clinical characteristics are shown in Table 1.

Data Analysis

By end of study period, 27.0% of patients with NC were dead versus 27.2% CAC patients. The median time-to-mortality was 14 days in the NC versus 10 days in the CAC group (Figure 1). In the multivariable analysis we found that NC infection was associated with reduced mortality (aHR=0.71, 95%CI 0.51-0.99; p=0.04, Table 2). It was also found that increased mortality was associated with: older age (compared to under 65, aged 65-79, aHR=2.70, 95%CI 1.91-3.81, p<0.001; aged ≥80, aHR=3.30, 95%CI 2.28-4.78, p<0.001); increased frailty (CFS=3-4, aHR=1.67, 95%CI 1.07-2.60, p=0.02; CFS=5-6, aHR=2.08, 95%CI 1.31-3.31, p=0.002; CFS=7-9, HR=2.75, 95%CI 1.73-4.38, p<0.001), renal failure (aHR=1.32; 1.07-1.63) and increased CRP (aHR=1.004, 95%CI 1.003-1.005, p<0.001) [Table 2].

In multivariable analysis for Day 7 mortality, there was no association between NC infection and mortality (aOR=0.89, 95%CI 0.60-1.34, p=0.59, Table 3. Important factors associated with Day 7 mortality were: increased age (compared to under 65, aged 65-79, aOR=3.12, p<0.001; aged ≥80, aOR=3.99, p<0001); increased CRP (aOR=1.006, p<0.001); reduced renal function (eGFR<60, aOR=1.95, p<0.001); CAD (aOR=1.59, p=0.01); and increased frailty (compared to CFS1-2: CFS 7-9, aOR=3.62, P<0.001).

Median length of stay for CAC patients was half that of NC patients (16 days versus 33 days, aHR=0.49, 0.37-0.66, p<0.001, Table 3). Covariates associated with an increased length of stay for all patients were: increased age (compared to under 65, aged 65-79, aHR=0.80; aged ≥80, aHR=0.61, p<0.001); worsening frailty (compared to CFS1-2, CFS 5-6, 0.73, p=0.02; CFS 7-9, aHR=0.70, p=0.02); and elevated CRP (aHR= 0.997, p<0.001).
The multivariable mixed effects Cox regression exploratory analyses of the time-to-mortality show consistent findings for NC versus CAC within each of the demographic and comorbidity subgroup analysis (Supplementary Figure 1).

Discussion

Statement of principal findings

This study is the first to report outcomes for patients with NC infection. Of all COVID-19 cases included 12.5% of infections were due to transmission in hospital. Overall mortality rate was 27.2% with a reduction in mortality with an NC infection. Patients with NC infection experienced a longer length of stay in hospital.

The strengths and weaknesses of the findings in relation to other studies

The proportion of nosocomial infections with COVID-19 found within this study was lower than the 41% previously reported by Wang and colleagues (15). Although direct comparisons are difficult, Wang had a small sample size (total 138 patients) which included healthcare worker infections. Excluding these, the rate of patient NC infection was similar to our study (12.3% versus 12.5%).

Compared to other reported rates of NC infection during historical global pandemics, it appears that NC infection rates are much lower during the COVID-19 pandemic, with the majority of in-hospital COVID cases originating from the community.

In western healthcare, infection control policies have been developed for many years which have positively impacted the response to the rapidly evolving pandemic situation. This multicentre study is predominantly UK based and it is important to recognise that data from eastern populations may not be applicable to western populations based upon individual genetic differences, available healthcare resources and preparedness of healthcare providers to respond to overwhelming demands on services. The first COVID-19 positive patient was reported to the World Health Organisation (WHO) on 31st December in Wuhan, China. The UK and Italy reported their first cases on 31st January 2020. It is possible that countries affected later were able to anticipate resources required and recognised the importance of being able to implement those plans quickly and have a different NC rate. This allowed patients with either diagnosed or suspected to have COVID-19 to be isolated, managed with an increased awareness of cross infection, with preventative measures such as personal protective equipment, in dedicated 'COVID-19' wards.

The public health message during the United Kingdom's lockdown was to stay at home, leaving home only for essential travel, in order to maintain social distancing measures. Understandably there is much anxiety amongst the general public, particularly amongst those with pre-existing healthcare conditions. This has led to 29% fewer ED attendances reported in March 2020 compared to March 2019 in England alone (29). Furthermore, the Office for National Statistics (ONS) reported the highest death rate in England & Wales since 2000 (week ending 3rd April 2020), 6,082 more than the 5-year average. Worryingly only 3,475 of these are attributed to COVID-19 (30), raising the concern that these additional deaths may have been related to a public reluctance to seek medical attention. Our findings have demonstrated that mortality rates are no worse if COVID-19 was acquired in hospital, compared with those who have acquired the disease in the community. Highlighting that patients should be reassured when seeking medical attention for non-COVID-19 conditions.

This NC group of patients were older and frailer, with a non COVID-19 pre-existing reason for hospital admission, all leading to and a median hospital stay in excess of one month. With daily inpatient assessment it is likely that prompt recognition of COVID-19 like symptoms occurred leading to prompt laboratory and clinical diagnosis of COVID-19 infection. In contrast the CAC patients may have tolerated their symptoms at home for a period of time before requiring hospital admission. There is also a possibility that reluctance to seek medical attention may have compounded their potentially delayed presentation to hospital. This difference in clinical management may have led to the NC patients to have timely supportive treatment, as opposed to

those coming in from home who may have presented late with more severe illness led to a reduced mortality in the CAC patients. It is possible that normal targeted and individualised care for longer term patients were reconfigured to focus on acute admission assessment and critical care. Although not assessed in this study and difficult to assess objectively, the influence of nursing in isolation and prohibition of hospital visitors is likely to have had a negative psychological impact for this patient group.

Strengths and weaknesses of the study

This is a large multicentre observational cohort study including over 1,500 adult in patients. Our definition of NC was conservative, so the infection rate should be considered 12.5% or greater. Since hospital workers or patient visitors with COVID-19 were not included in the definition of NC infection, or were patients with a positive diagnosis less than 15 days prior to their admission. Or asymptotic patients were discharged without a positive diagnosis (most likely in younger or less severe patients). A further limitation of this observational study is that we could not allow for case-mix differences between the NC and CAC groups, including mildly symptomatic or asymptomatic patients diagnosed COVID-19 as part hospital screening programmes. Furthermore, we did not assess the cause of death for patients from both NC and CAC groups, although it is assumed that COVID-19 formed at least part of the cause of death for all those who died.

Impact on clinical practice, public health and policymakers

With low hospital acquired infection rates, this study demonstrates that effective infection control policies are in place in western hospitals. It is now the responsibility of public and professional bodies to actively encourage patients to seek acute medical attention when required and to consider the risks and benefits of reintroducing elective services. Organisational response to emerging evidence should be proactive, considered and continuous. It is imperative that complacency is avoided in response to reduced published daily mortality figures in order to prevent a second wave.

Conclusion

In a large study, we found that the minority of COVID-19 hospital episodes were the result of nosocomial transmission. Whilst no COVID-19 infection comes without risk, those patients with NC infection had no greater risk of mortality, and potentially lower risk than people admitted to hospital with COVID-19.

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Declarations and disclosures

The Patient and Public Involvement statement

The Older Person's Surgical Outcomes Collaboration (OPSOC) over the last seven years have engaged with patients over study design, interventions, and dissemination. The COPE study was discussed by patients at the study set up about the outcomes to be collected at the protocol stage. This particular study was set up, and conducted in a timely manner, to address if attending hospital during the first (or subsequent) waves of the epidemic was likely to lead to infection, and if that infection would have an increased risk of experiencing a clinical event.

Role of the funding source:

There was no funding for the COPE study.

Conflicts of Interest

No conflicts exist from any of the authors

Contribution of authors

BC, JH, KM, conceived the study, AP, AVM, BC, EM, FBP, JH, LP, KM, PB, PM, SM developed the protocol, AP, AV, AVM, AE, EB, EM, JTC, FPB, FR, JH, PB, TQ and all collaborators collected data, BC, RS carried out the analysis, RS generated the graphics, BC, FBP, JTC, FR, JH, MS, KM, PM, TQ, SM interpreted the findings, BC, JH, KM, LP, RS, SM and JTC drafted the manuscript. All authors reviewed the final manuscript.

JH is Chief Investigator of the COPE study and guarantor of all COPE analyses

Competing interest and disclosures statement

No author has a competing interest to declare

Data Sharing Statement

Data is available to researchers to address pre-planned hypotheses by request from the COPE Study investigators.

Table 1 Demographics, frailty and nosocomial infection, by mortality

	Dead	Alive	Total
Sites[&]	**425 (27.2%)**	**1,139 (72.8%)**	**1,564**
Hospital A	15 (13.0)	100 (87.0)	115 (7.4)
Hospital B	14 (28.0)	36 (72.0)	50 (3.2)
Hospital C	34 (22.2)	119 (77.8)	153 (9.8)
Hospital D	10 (23.3)	33 (76.7)	43 (2.8)
Hospital E	15 (12.2)	108 (87.8)	123 (7.9)
Hospital F	23 (14.9)	131 (85.1)	154 (9.9)
Hospital G	36 (32.1)	76 (67.9)	112 (7.2)
Hospital H	108 (43.9)	138 (56.1)	246 15.7)
Hospital I	126 (33.2)	254 (66.8)	380 (24.3)
Hospital J	43 (24.0)	136 (76.0)	179 (11.5)
Hospital K	1 (11.1)	8 (88.9)	9 (0.6)
Age			
Under 65 yrs	55 (11.3)	433 (88.7)	488 (31.2)
65 to 79 yrs	168 (31.4)	367 (68.6)	535 (34.2)
Over 80 yrs	202 (37.3)	339 (62.7)	541 (34.6)
Sex			
Female	170 (25.7)	491 (74.3)	661 (42.3)
Male	255 (28.2)	648 (71.8)	903 (57.7)
Smoking Status			
Never smokers	205 (25.2)	609 (74.8)	814 (52.9)
Ex smokers	185 (30.7)	418 (69.3)	603 (39.2)
Current smokers	26 (21.5)	95 (78.5)	121 (7.9)
Missing	9	17	26
CRP[&&]	113, (64-185)	71, (30-137)	83, (37-153)
eGFR > 40			
No	202 (20.6)	778 (79.4)	980 (63.2)
Yes	217 (38.1)	353 (61.9)	570 (36.8)
Missing	6	8	14
Hypertension			
No	184 (24.4)	571 (75.6)	755 (48.4)

Yes	238 (29.6)	566 (70.4)	804 (51.6)
Missing	3	2	5
Coronary Artery disease			
No	290 (23.9)	924 (76.1)	1214 (77.9)
Yes	132 (38.3)	213 (61.7)	345 (22.1)
Missing	3	2	5
Diabetes			
No	295 (25.8)	849 (74.2)	1144 (73.2)
Yes	128 (30.8)	287 (69.2)	415 (26.6)
Missing	2	3	5
COVID-19 Infection			
Community acquired	372 (27.2)	996 (72.8)	1368 (87.5)
Nosocomial acquired	53 (27.0)	143 (73.0)	196 (12.5)
Clinical Frailty Score (CFS)			
1, Very Fit	7 (7.7)	84 (92.3)	91 (5.8)
2, Fit	22 (11.2)	175 (88.8)	197 (12.6)
3, Managing well	55 (19.2)	232 (80.8)	287 (18.4)
4, Vulnerable	52 (28.1)	133 (71.9)	185 (11.9)
5, Mildly frail	50 (27.5)	132 (72.5)	182 (11.7)
6, Frail	84 (33.5)	167 (66.5)	251 (16.1)
7, Severely frail	96 (36.9)	164 (63.1)	260 (16.7)
8, Very severely frail	44 (55.7)	35 (44.3)	79 (5.1)
9, Terminally ill	12 (44.4)	15 (55.6)	27 (1.7)
Missing	3	2	5

[&]Note: Hospitals are anonymised; [&&]Presented as median (IQR)

Table 2 – Primary outcome: Crude and Adjusted Time-to-mortality, from admission (or diagnosis, for patients with a diagnosis five or more days after admission). Survival is estimated with a crude hazard ratio (HR), and adjusted Hazards Ratio (aHR), using a crude and adjusted mixed-effects multivariable Cox proportional hazards regression.

	Crude Hazard ratio (HR)		**Adjusted HR (aHR)[&]**	
	(n=1,520)[&&]		**(n=1,500)[&&&]**	
	HR, (95%CI)	p-value	aHR, (95%CI)	p-value
Location infection acquired				
Community acquired (Ref)	Reference Category		Reference Category	
Hospital acquired	0.71, (0.52-0.97)	0.03	0.71, (0.51-0.98)	0.04
Age				
Under 65	Reference Category		Reference Category	
65 to 79	3.30, (2.40-4.55)	<0.001	2.70, (1.91-3.81)	<0.001
Over 80	4.05, (2.95-5.57)	<0.001	3.30, (2.28-4.78)	<0.001
Sex (Female)	Reference Category		Reference Category	
Male	0.99, (0.81-1.21)	0.93	1.10, (0.89-1.37)	0.38
Smoking status (Never)	Reference Category		Reference Category	
Ex-smokers	1.20, (0.98-1.47)	0.08	0.95, (0.76-1.17)	0.61
Current smokers	0.84, (0.55-1.29)	0.43	1.09, (0.70-1.70)	0.71
CRP[$]	1.003, (1.002-1.004)	<0.001	1.004, (1.003-1.005)	<0.001
Patients with diabetes	1.12, (0.90-1.39)	0.30	1.03, (0.82-1.30)	0.77
Patients with CAD	1.57, (1.26-1.95)	<0.001	1.21, (0.96-1.53)	0.10
Patients with hypertension	1.24, (1.01-1.51)	0.04	0.98, (0.80-1.22)	0.89
Patients with reduced renal function				
	1.93, (1.58-2.35)	<0.001	1.32, (1.07-1.63)	0.01
Clinical Frailty Scale				
CFS 1 to 2	Reference Category		Reference Category	
CFS 3 to 4	2.25, (1.47-3.45)	<0.001	1.67, (1.08-2.60)	0.02
CFS 5 to 6	3.12, (2.05-4.76)	<0.001	2.08 (1.31-3.32)	0.002
CFS 7 to 9	4.41, (2.90-6.71)	<0.001	2.75, (1.73-4.38)	<0.001

[&]The multivariable mixed-effects Cox regression was adjusted for: age group; sex; smoking; CRP; diabetes; CAD; hypertension; and the Clinical Frailty Scale
[&&]44 Cases were not included in the analysis due to patient death on admission.
[&&&]20 Cases were not included in the analysis due to missing covariate data-see Table 1.
[$]fitted as a slope parameter

Table 3**:** Secondary Outcomes. Outcome 1: Day-7 mortality (Left panel), estimated with an adjusted Odds Ratio (aOR) and analysed using an adjusted mixed-effects multivariable logistic model. Outcome 2: Length of hospital stay (Right panel) (measured as the time to discharge from admission, or diagnosis for patients with a diagnosis five or more days after admission), estimated with an adjusted Hazards Ratio (aHR) and analysed with an adjusted mixed-effects multivariable Cox proportional hazards regression.

	Day 7 Mortality		**Length of Hospital Stay**	
	Adjusted Odds ratio (aOR)		**Adjusted HR (aHR)[&]**	
	(n=1,494)[&&]		**(n=1,500)[&&&]**	
	HR (95%CI)	p-value	aHR (95%CI)	p-value
Location infection acquired				
Community acquired (Ref)	Reference Category		Reference Category	
Nosocomial	0.79 (0.47-1.31)	0.35	0.49 (0.37-0.66)	<0.001
Age				
Under 65	Reference Category		Reference Category	
65 to 79	3.12 (1.83-5.33)	<0.001	0.80 (0.66-0.97)	0.03
Over 80	3.99 (2.25-7.08)	<0.001	0.61 (0.48-0.78)	<0.001
Sex (Female)	Reference Category		Reference Category	
Male	1.13 (0.80-1.58)	0.50	093 (0.79-1.09)	0.36
Smoking status (Never)	Reference Category		Reference Category	
Ex-smokers	1.09 (0.78-1.53)	0.61	0.97 (0.82-1.14)	0.70
Current smokers	0.98 (0.49-1.99)	0.96	1.03 (0.76-1.41)	0.83
CRP[$]	1.01 (1.005-1.008)	<0.001	0.997 (0.996-0.998)	<0.001
Patients with diabetes	1.00 (0.69-1.44)	0.99	0.94 (0.78-1.13)	0.50
Patients with CAD	1.59 (1.11-2.28)	0.01	1.09 (0.89-1.35)	0.39
Patients with hypertension	0.86 (0.61-1.21)	0.38	0.91 (0.77-1.07)	0.24
Patients with reduced renal function				
	1.95 (1.39-2.73)	<0.001	0.91 (0.76-1.09)	0.32
Clinical Frailty Scale				
CFS 1 to 2	Reference Category		Reference Category	
CFS 3 to 4	1.28 (0.65-2.52)	0.48	0.94 (0.77-1.16)	0.58
CFS 5 to 6	1.86 (0.91-3.79)	0.09	0.73 (0.56-0.96)	0.02
CFS 7 to 9	3.62 (1.78-7.34)	<0.001	0.70 (0.53-0.94)	0.02

[&] The multivariable mixed-effects logistic and cox regressions were adjusted for: age group; sex; smoking; CRP; diabetes; CAD; hypertension; and the Clinical Frailty Scale
[&&] 6 cases were excluded from the analysis as the patient was followed up for less than 7 Days and alive and in hospital
[&&&] 20 cases were not included in the analysis due to missing covariate data-see Table 1

Figure 1: Kaplan Meier Survival plot of nosocomial versus community Infection of COVID-19 patients

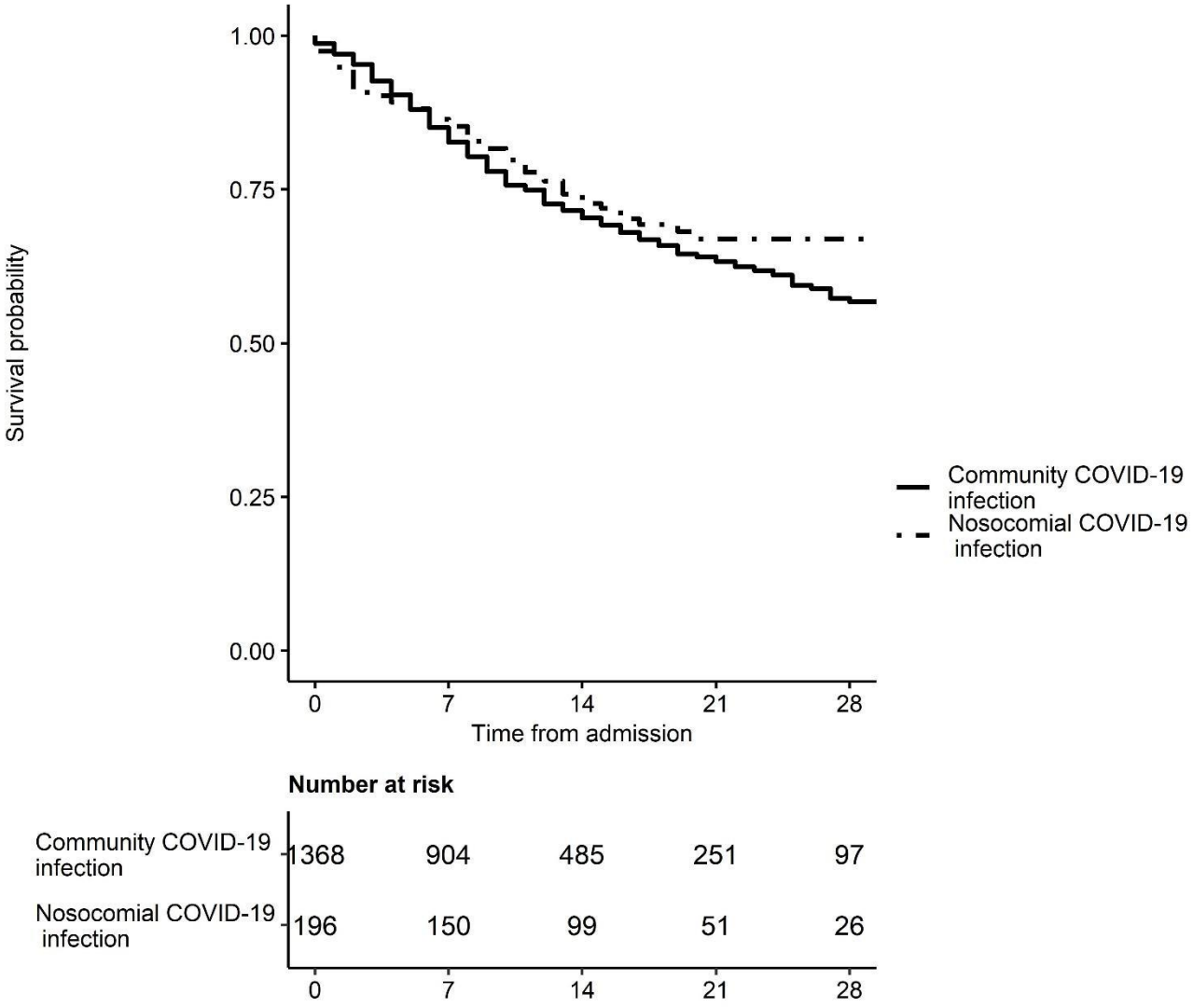
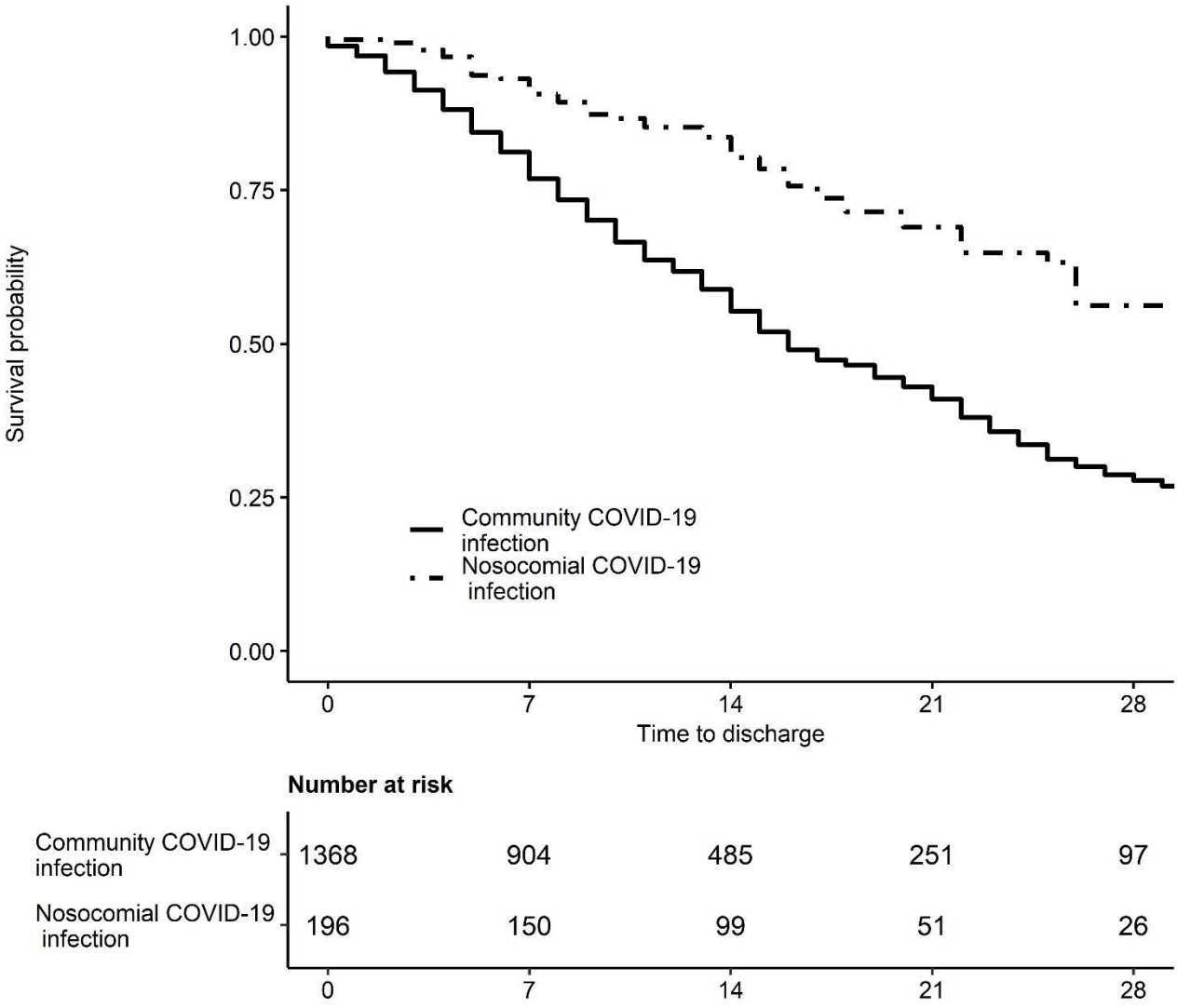
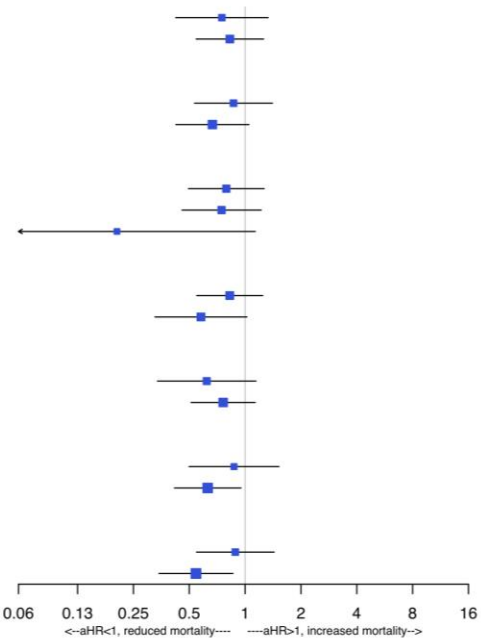


Figure 2: Kaplan Meier Survivor Plot for time–to–discharge for nosocomial verses community infection.



Supplementary Figure 1: Time to mortality analysis, carried out in each subgroup. The findings present the adjusted multivariable Hazard Ratio for patients with a Nosocomial Infection versus a Community acquired COVID-19 infected patients

Subgroup	NC infection n/N (%)	Adjusted Hazard Ratio (95% CI)	P
Age			
Under 65*	31/488 (6.4)		
65-79	60/535 (11.2)	0.75 (0.42-1.33)	0.32
80 years and over	105/541 (19.4)	0.83 (0.54-1.26)	0.38
Sex			
Female	98/661 (14.8)	0.87 (0.53-1.41)	0.56
Male	98/903 (10.9)	0.67 (0.42-1.05)	0.08
Smoking			
Never smoked	96/840 (11.4)	0.79 (0.50-1.27)	0.33
Ex-smoker	73/603 (12.1)	0.75 (0.46-1.22)	0.24
Current smoker	27/121 (22.3)	0.20 (0.04-1.13)	0.07
Hypertension			
Yes	105/804 (13.1)	0.83 (0.55-1.25)	0.36
No	90/755 (11.9)	0.58 (0.33-1.02)	0.06
Diabetes			
Yes	55/415 (13.3)	0.62 (0.34-1.14)	0.13
No	140/1144 (12.2)	0.76 (0.51-1.13)	0.18
CAD			
Yes	49/345 (14.2)	0.87 (0.50-1.52)	0.63
No	146/1214 (12.0)	0.63 (0.42-0.95)	0.03
Kidney function			
eGFR<60	65/570 (11.4)	0.89 (0.55-1.43)	0.62
eGFR>=60	125/980 (12.8)	0.54 (0.34-0.86)	0.01



Note: Multivariable analyses adjusted for age group, sex, smoking status, hypertension, diabetes, CAD, kidney function, CRP and CFS. *Subgroup omitted due to low number of observations.