Does nosocomial SARS-CoV-2 infection result in increased 30-day mortality? A multi-centre observational study to identify risk factors for worse outcomes in COVID-19 disease.

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Conflict of Interest

All authors have no conflicts of interest or financial ties to disclose.

Abbreviations:

WHO - World Health Organization

COPD - Chronic obstructive pulmonary disease

ACCI - Age-adjusted Charlson co-morbidity index

SIMD - Scottish Index of Multiple Deprivation

CRP - C-reactive protein

RT-PCR - Reverse transcription polymerase chain reaction

NHS - National Health Service

CXR - chest X-ray

BSTI - British Society of Thoracic Imaging

eGFR - Estimated glomerular filtration rate

LOS - Length of stay

ITU - Intensive treatment unit

PHE - Public Health England

ABSTRACT

Objective

We aimed to determine whether nosocomial SARS-CoV-2 infection has worse outcomes than community-acquired disease and to identify demographic, biochemical and investigational predictors for severe disease.

Design

Prospective cohort study. Patients were followed up for at least 30 days.

Setting

Three acute hospitals in a single NHS trust.

Patients

All hospitalised patients with confirmed COVID-19 on 9th April 2020.

Methods

Nosocomial infection was defined as positive swab after 7 days of admission. Baseline characteristics, investigation findings and patient level of care were analysed. We explored whether these variables were predictive of poor outcomes including increased length of stay (LOS), critical care admission, and death.

Results

173 patients were identified, 19 (11.0%) had nosocomial infection. 32 (18.5%) had 30-day all-cause mortality; there was no statistically significant differences between 30-day mortality rates between nosocomial infection and those admitted due to, or incidentally with SARS-CoV-2 infection (21.1% vs 17.6% vs 21.6% respectively, p=0.755). Admission blood profile and chest X-ray findings were also not predictive of mortality. The age-adjusted Charlson comorbidity index (ACCI), Scottish Index of Multiple Deprivation (SMID) and admission to critical care were all significant

predictors of LOS ($p<0.05$). In patients who did not attend critical care, male (HR=3.36, $p<0.05$) and high ACCI (HR=1.29, $p<0.05$) were predictors of mortality.

Conclusions

Nosocomial SARS-CoV-2 infection is not associated with increased mortality compared with community acquired infection. ACCI score and male sex are predictors of poor outcomes. SMID is a predictor of LOS but not mortality.

Keywords

SARS-CoV-2, pandemic, socioeconomic deprivation, 30-day mortality, co-morbidities, outcomes.

INTRODUCTION

In December 2019 a series of viral pneumonia cases were reported in Wuhan, Hubei province, China. The World Health Organization (WHO) named the novel coronavirus SARS-CoV-2 as the causative virus of the disease COVID-19. On 30 January 2020, the WHO declared that this viral outbreak constituted a Public Health Emergency of International Concern. The spectrum of disease severity is wide, generally around 81% of cases are mild, 14% severe and 5% critical, with outcomes influenced by a range of factors.[1] No vaccine is available and the mainstay of treatment for COVID-19 is supportive.[2]

All age groups are susceptible, but elderly patients are more likely to have severe disease.[1] Co-morbidities that increase mortality have been well described in recent literature. The Age-adjusted Charlson co-morbidity index (ACCI) is a widely used prognostic indicator that assesses risk conferred by age and co-morbid disease and allows a more pragmatic approach to comparisons within populations. The Scottish Index of Multiple Deprivation (SIMD) is a relative measure of 7 domains (income, employment, education, health, access to services, crime and housing) used to target policies and funding to more deprived areas.

Whilst the median incubation period of SARS-CoV-2 infection is around 4 days (range 1-14 days), patients can be contagious before the onset of symptoms and the duration of infectivity remains uncertain.[2]

Our primary aim was to determine whether nosocomial SARS-CoV-2 infections increased mortality rates compared with community-acquired disease after adjusting for covariates. Our secondary aim was to identify demographic and other risk factors for severe SARS-CoV-2 infection outcomes.

METHODS

Study Design and Participants

A prospective cohort study was conducted on all hospitalized patients with reverse transcription polymerase chain reaction (RT-PCR) confirmed SARS-CoV-2 infection, on a single day. This was carried out across three acute hospitals in a single National Health Service (NHS) Trust in Scotland serving a population of 655,000.

Data collection

Patients with positive RT-PCR swabs were identified from TrakCare Electronic Medical Record System. Demographic data, SIMD score and ACCI were extracted from electronic case records.

Patients were categorised into three distinct groups based on the reason of admission: group 1 were admitted with suspicion of SARS-CoV-2 infection, group 2 presented with other pathologies but were incidentally found to have SARS-CoV-2 infection on admission (or within 7 days of admission), and group 3 were admitted with other pathologies and contracted COVID-19 infection in hospital (positive RT-PCR after 7 days of admission). In patients with nosocomial SARS-CoV-2 infection, day 0 was defined as the date of positive RT-PCR. All patients were included in the study and followed up for 30 days from admission or until discharge or death.

Outcome measures

We defined a poor outcome as including all cause 30-day mortality and/or need for critical care admission. Baseline characteristics were compared between survivors/non-survivors.

Statistical analyses

Length of stay (LOS) was calculated from the date of positive COVID-19 diagnosis until discharge or death. Covariates controlled for included ACCI, sex, deprivation decile and transfer to critical care. Age was not included as this is included in the ACCI.

Multivariate logistic regression was performed to explore predictors of transfer to critical care. Only group 1 was included in this analysis due to a lack of data in groups 2 and 3. Covariates included in this analysis were ACCI, sex and deprivation decile. ACCI was categorised as either a low (ACCI = 0-3) or high (ACCI = 4+).

A p value of <0.05 was considered statistically significant.

This study was registered with the NHS Lanarkshire's Clinical Quality Project, project ID: 13124.

RESULTS

We identified 173 patients of whom 108 (62.4%) were male, with a mean (SD) age of 68 (14.7) years. Of these, 31 (17.9 %) died within 30-days of positive RT-PCR. Median time to acquire nosocomial COVID-19 infection was 35 days (IQR = 18, 42). Summary baseline patient characteristics for each admission group were calculated and differences explored with univariate analyses (***table I***). There was no significant difference in mortality between the groups. ***Figure I*** shows a Kaplan-Meier plot of Groups 1, 2 and 3 (unadjusted).

Length of stay

Data on length of stay is reported only for those patients primarily admitted for treatment of COVID or who had incidental COVID on admission (groups 1 and 2). Admission type was not a predictor of LOS, although ACCI ($p<0.001$), admission to critical care ($p<0.001$) and deprivation decile ($p<0.05$) were all significant predictors of LOS. Beta estimates and confidence intervals for each covariate can be found in the additional file.

Critical care admission

The overall model was significant ($\chi2=22.98$, df = 3, $p<0.001$) and 70.0% accurate. Of the included covariates, only ACCI was significant (OR=0.114, $p<0.001$) suggesting that patients with a higher ACCI were less likely to be admitted to critical care (***additional file***).

Survival analysis

Analysis of 30-day mortality was stratified by critical care admission. Out of 125 patients not attending critical care, there were 19 deaths within 30 days. For this cohort, a Cox's PH model showed both ACCI (HR=1.29, $p<0.05$) and male sex (HR=3.36, $p<0.05$) were predictive of 30-day mortality. Neither admission status nor deprivation decile were found to be significant. Among 48 patients who attended critical care, there were 13 deaths within 30 days of diagnosis. Neither ACCI nor sex were significant predictors of mortality in this group. The small sample size, however, means results from this model should be interpreted with caution. Survival curves for these groups are available in the additional file.

DISCUSSION

Patients in our hospital-based population had a 30-day mortality rate of 18.5%. Our study shows that male sex and ACCI score were predictive factors for 30-day mortality in those not attending critical care. We also found SMID and ACCI scores to be predictive of LOS.

Importantly we have shown that nosocomial COVID-19 is not associated with increased mortality after adjusting for ACCI score. This is likely to be reflective of other parts of the UK. There have been over 15,000 positive cases to date (end May 2020) in Scotland with approximately a 15% (versus our 18.5%) case fatality rate.[3] This lower figure is likely representative of the increased acuity of hospitalised patients compared with the national population.

Male sex was associated with poor outcomes as seen in previous studies,[2] no patients with an ACCI score of ≤1 died, yet those with a score ≥2 had a greater than 25% chance of mortality. The median ACCI score in this study was 4 equating to an estimated 53% 10-year survival representing a very high comorbid disease burden in our study population. Similar results have been reported where the incidence of co-morbidities was higher in COVID-19 patients than the general age-matched population.[7] Our finding that patients with a higher ACCI score were less likely to be admitted to critical care is expected as they may be less likely to be accepted for ITU admission due to the perceived high chance of non-survival. Interestingly, male sex was a predictor of mortality only in those patients who were not admitted to critical care.

Recent unpublished statistical modelling performed by Public Health England (PHE) predicts approximately 20% of hospital inpatient SARS-CoV-2 infections are nosocomial.[8] Only 11% of cases in our study were nosocomial, and stringent isolation practices already implemented may explain these low relatively low results. Furthermore, our hospitals were not fully saturated with COVID-19 during the pandemic, and during our study only 55% of beds were occupied (excluding critical care). This may in part explain lower COVID-19 nosocomial infection rates than predicted by PHE.

In our study, there was a 21.1% 30-day mortality rate among patients with nosocomial infection compared to 17.6% in those presenting with COVID-19, though our analysis does not suggest that this is statistically significant. However, our sample size was small, and results should be interpreted with caution. Compared with patients admitted with symptomatic SARS-CoV-2 infection, patients with nosocomial infection were significantly older and had higher ACCI scores. This indicates an ongoing risk for vulnerable patient groups such as has been demonstrated by care homes across the UK.

One of the greatest challenges with COVID-19 infection is that it can present with a wide spectrum of illness, including symptoms similar to those of common respiratory viruses, or may be entirely asymptomatic, increasing risks of nosocomial infection. This presents challenges for availability of isolation and containment rooms in busy hospitals, and many patients admitted without suspicious contact history or characteristic presenting symptoms of COVID-19 may receive care outside dedicated isolation areas.

The initial cross-sectional method of participant identification in this study enables a valid representation of the hospital population in this health board and data was collected across all departments. However, this method will be subject to a degree of length-time bias as patients with longer hospital stays would be more likely to be picked up by this method of identification leading to inaccurate measures of survival / discharge.

A key limitation to this study is the small sample size. Our group sizes were not equal, we only recruited 19 nosocomial infections for analysis, which made it difficult to confidently analyse differences. Collecting data in more than one region and recruiting a greater sample size with a control population, would improve the validity and generalisability of the data.

There is currently no WHO approved definition for nosocomial infection. A cut off as 4 days after initial hospitalisation and the absence of clinical suspicion of COVID-19 has been utilised previously.[9] As the incubation period could be up to 14 (IQR 2-7) days, it is difficult to be certain that an infection was acquired in hospital. [2]

Nosocomial infections may be less advanced when they are detected due the heightened awareness of COVID-19 symptoms by healthcare workers. This means we may identify more mild cases in group 3 in comparison to those requiring hospital admission in groups 1 and 2. Conversely, at the time of data collection, only patients who were symptomatic were tested in hospital, meaning there may have been a greater number of asymptomatic nosocomial infections who would've been included in Group 3. Patients in groups 1 and 2 may have different thresholds for self-presentation to hospital. This means our defined day 0 may vary between patients.

We did not include group 3 in our length of stay analysis as by definition they had

already been admitted to hospital for a minimum of 7 days for other pathologies making LOS comparison with those admitted with SARS-CoV-2 infection impossible.

Our study demonstrates that nosocomial SARS-CoV-2 infection is not associated with a statistically significant increase in 30-day mortality compared with community acquired infection. Male sex, age and ACCI score are significant predictors of mortality in the whole cohort. A high degree of vigilance will be required by all members of the healthcare team to prevent the spread of SARS-CoV-2 within hospitals. Nosocomial infection poses an important challenge to vulnerable hospital populations, and needs to be considered as the NHS attempts to resume elective activities, balancing the risks and benefits whilst the COVID-19 pandemic continues. Our study shows a relatively low risk of contracting COVID-19 infection in hospital with comparable outcomes to when the disease was contracted in the community. Further studies are essential to identify the mechanisms and to gain a greater understanding of how certain risk factors influence outcomes with COVID-19 disease in order to guide public health initiatives aimed to shield at risk groups and save lives.

References

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA - J Am Med Assoc. 2020;
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;
3. The Scottish Government. Coronavirus (COVID-19): daily data for Scotland [Internet]. 2020 [cited 2020 Jun 10]. Available from: https://www.gov.scot/publications/coronavirus-covid-19-daily-data-for-scotland/
4. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020;368.
5. Park SY, Kim JY, Kim J, Kwon J, Kim S, Jeon NY. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China (2019): a single-centered, retrospective study. J Gerontol A Biol Sci Med ScI. 2020;
6. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. Jama. 2020;10022:1–8.
7. Wang L, He W, Yu X, Hu D, Bao M, Liu H, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;(January).
8. Evans S, Agnew E, Vynnycky E, Robotham J. The impact of testing and infection prevention and control strategies on within-hospital transmission dynamics of COVID-19 in English hospitals Methods Model Description. 2020;
9. Van Praet JT, Claeys B, Coene A-S, Floré K, Reynders M. Prevention of nosociomial Covid-19: another challenge of the pandemic. Infect Control Hosp Epidemiol. 2020;1–4.

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CONFLICT OF INTREST

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REFERENCES

Table I –Baseline characteristics and main outcomes: Analyses performed included one-way ANOVA (age), Fisher's Exact Tests (sex, ITU attendance, death) and Kruskal-Wallis tests (ACCI, deprivation decile).

	Total	Group 1	Group 2	Group 3	P value
Total patients	173	131	23	19	*NA*
Mean age (SD)	68.44 (14.7)	66.14 (13.8)	78.39 (10.0)	72.26 (19.3)	**<0.001**
Male (%)	108 (62.4)	90 (68.7)	9 (39.1)	9 (47.4)	**<0.01**
Median ACCI (IQR)	4 (2, 6)	3 (2, 5)	6 (4.5, 7)	5 (4, 7)	**<0.001**
Median deprivation decile (IQR)	4 (2, 6)	5 (2, 7)	3 (2, 5)	4 (3, 5.5)	0.321
Attended critical care (%)	48 (27.7)	45 (34.4)	1 (4.3)	2 (10.5)	**<0.01**
30-day mortality	32 (18.5)	23 (17.6)	5 (21.7)	4 (21.1)	0.755

ITU = Intensive Treatment Unit, ACCI = Age-adjusted Charlson Co-morbidity Index, SD= Standard Deviation, IQR = Interquartile Range.

FIGURE LEGENDS

Figure 1 - Kaplan-Meier plot stratified by admission group (Group 1 = admitted for SARS-CoV-2 infection, group 2 = incidental Sars-Cov-2 infection, group 3 = nosocomial Sars-Cov-2 infection).