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# The Impact of the COVID-19 Pandemic on Healthcare Associated Bloodstream Infections in Scottish Intensive Care Units: a Retrospective Cohort Study

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# Statements and Declarations

## Ethical Considerations

This study was undertaken by ARHAI Scotland, National Services Scotland (NSS), as part of its duty to monitor and investigate healthcare associated infections. This study is classified as health surveillance under the UK Policy Framework for Health and Social Care Research set out by the NHS Health Research Authority, and thus ethical review is not required.[12]

## Consent to Participate

Individual patient consent is not required for ARHAI Scotland to process personal data to conduct specific statutory tasks within the public interest, as set out in NSS 's Data Protection Notice.[13] Linkage of existing datasets was approved by Public Health Scotland via a Data Release Linkage Form.

## Consent for Publication

Not applicable.

## Declaration of Conflicting Interest

All authors declare no potential conflicts of interest with respect to the research, authorship and publication of this article.

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## Data Availability

We are not permitted to share the datasets used during this study directly, according to NHS data governance policy. However, researchers can request access from the Scottish Public Benefits and Privacy Protection Committee at Public Benefit and Privacy Panel for Health and Social Care (scot.nhs.uk).

# Abstract

## Background

Healthcare associated blood stream infections (BSI) pose a significant risk of morbidity and mortality for patients admitted to intensive care units (ICUs). Recent evidence suggests that the COVID-19 pandemic may have impacted the risk of acquisition.

## Aim

This retrospective cohort study explored risk factors, including patient COVID-19 admission status, associated with incidence rates of BSI in Scottish ICUs during the COVID-19 pandemic compared to a pre-pandemic period.

## Methods

Three national databases were linked to create a dataset of 38,081 ICU admissions across 41 ICUs during a comparator period of March 2018 to December 2019, and pandemic period of March 2020 to December 2021. Population demographics and clinical risk factors were described according to period of admission and COVID-19 admission status. Cox regression models investigated the influence of risk factors on time to BSI, using a competing risk approach to account for death as a competing event.

## Findings

In non-COVID-19 patients, the first two waves of the pandemic significantly increased hazards of BSI (Wave 1 cause-specific hazard ratio (HR) 1.27, 95% Confidence Interval (CI) 1.02-1.59, wave 2a HR 1.39, 95% CI 1.14-1.70), but not mortality. COVID-19 status on admission did not significantly increase hazard of BSI in the pandemic, however there was a significant interaction between COVID-19 and the use of intubation in increasing hazard of BSI (HR 4.64, 95% CI 2.07-10.4) and COVID-19 was significant in increasing the hazard of mortality (HR 2.26, 95% CI 1.77-2.88).

## Conclusion

While rates of ICU-acquired BSI were higher during the pandemic period, and in COVID-19 admissions, the reasons for this are multifactorial. Interpretation must consider the competing risk of mortality and how this is influenced by differences in patient population, along with changes that occurred during the pandemic in relation to infection prevention and control procedures, ICU pressures, and COVID-19 treatment and vaccination.

# Introduction

The COVID-19 pandemic has had a substantial impact on intensive care units (ICUs). The Scottish Intensive Care Society Audit Group (SICSAG) reported that the pandemic had resulted in a substantially different case-mix of patients admitted to ICUs, in conjunction with shortages of trained staff and equipment.[1] Healthcare associated infections (HAI), such as bloodstream infections (BSI), already posed a considerable risk to vulnerable patients, such as those requiring critical care, prior to the pandemic.[2] Recent evidence suggests that during the COVID-19 pandemic there was an increased rate of BSI acquired by ICU patients.[3-5] However, specific risk factors have been difficult to identify due to the complexity of interpreting HAI epidemiology in the presence of many possible confounding factors, including changes to patient demographics and clinical interventions.

In response to the pandemic, the COVID-19 Nosocomial Review Group (CNRG) was set up by the Scottish Government Chief Nursing Officer. During the lifetime of the group, ARHAI Scotland provided epidemiological data to the CNRG on non-COVID-19 healthcare associated infections, to support understanding of the wider situation in healthcare. The CNRG noted the risk from secondary bacterial infections at their meeting in October 2020, and ARHAI Scotland were asked to further investigate this.

This study builds on the analysis undertaken at the request of the CNRG, and aims to investigate the rates of ICU-acquired BSIs in Scotland prior to and during the pandemic, and the changing population and risk factors that may influence these rates. The objectives of the study were to:

I. Describe the characteristics of the patient population in Scottish ICUs during the pandemic and during an equivalent time-period preceding the pandemic; and describe the pandemic population subsets admitted with and without COVID-19.
II. Describe the most frequently isolated microorganisms within each of the populations detailed above.

III. Calculate the incidence of ICU-acquired BSIs in Scottish ICU patients during the pandemic, compared to in ICU patients during an equivalent time-period preceding the pandemic; and subset by those admitted with and without COVID-19.

IV. Use multivariate modelling to investigate demographic and available clinical risk factors influencing the likelihood of acquiring an ICU-acquired BSI in the presence of a competing risk of death.

# Methods

## Study Population

Included in the study were patients aged 16 years and over, admitted to any NHS Scotland ICU for three or more calendar days during two periods: the COVID-19 pandemic period - 1 March 2020 to 30 November 2021 (n=17,982); and a pre-pandemic comparator period - 1 March 2018 to 30 November 2019 (n=20,099). Each cohort had a 28-day follow-up period ending on 28 December 2021 and 2019, respectively. Where patient transfers occurred between ICUs, this was treated as one admission to a continuous ICU stay.

## Data Linkage

The study dataset was created via linkage of three national datasets by Community Health Index (CHI) unique patient identifiers. These datasets included: ICU admission data from the SICSAG critical care national database; positive blood culture and SARS-CoV-2 results from Electronic Communication of Surveillance in Scotland (ECOSS); and co-morbidity data from the Scottish Morbidity Records 01 General/Acute Inpatient and Day Case national dataset (SMR01).

## Case Definitions

A case of ICU-acquired BSI was defined as a positive blood culture for any bacterial or *Candida* species isolated from a patient on day three onwards of an ICU admission until two days after ICU discharge, who had not previously had the same organism isolated from blood within the same 14-day period.

Viruses and parasites were excluded from the BSI analysis. All fungi, apart from *Candida* species, were excluded due to issues with robustness of available data. Candidaemia were well reported in the national database and considered important in this population.

To align with the European Centre for Disease Prevention and Control (ECDC) BSI case definition, common skin contaminants (*Bacillus* species, *Corynebacterium* species, *Cutibacterium acnes*, *Dermabacter* species, *Dermacoccus* species, *Micrococcus* species, and coagulase-negative staphylococci) were included if reported in two separate blood specimens within three calendar days, as a proxy for BSIs.[6] Data on signs and symptoms of infection were not available, therefore we included skin contaminants as outlined, regardless of the presence of signs or symptoms.

A COVID-19 ICU admission was defined as ICU admission with laboratory confirmation of first SARS-CoV-2 positive (of any COVID-19 episode, including reinfections) during the 21 days before the date of ICU admission OR on day one or day two of admission.

## Descriptive Analysis

Descriptive analysis was undertaken for demographic variables and clinical data collected as part of routine healthcare associated infection surveillance.[7] These variables were: age group, sex, admission source (community or other hospital area), trauma admission, Charlson score at admission (derived from SMR01), admission type (medical, elective surgery, or emergency surgery), therapeutic antimicrobial use in the 48 hours before and/or after admission, mortality status on discharge from ICU, Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission, any central venous catheter (CVC) use during ICU stay, any intubation during ICU stay, and transfer directly between ICUs during the stay. A variable dictionary with detailed definitions can be found in Appendix A.

Time-period was used as a proxy for a number of features which varied before and during the pandemic, including the dominant SARS-CoV-2 variant,[8] as well as variations in infection prevention and control (IPC) procedures, healthcare system pressures, COVID-19 treatment and vaccine availability. The time periods were defined in alignment with surges of hospital onset COVID-19 infection.[9] Pandemic Wave 1 included admissions between 01-03-2020 and 31-07-2020 and discharged prior to 28-12-2021. Wave 2a included admissions between 01-08-2020 and 27-12-2020 and discharged prior to 28-12-2021. Wave 2b included admissions between 28-12-2020 and 17-05-2021 and discharged prior to 28-12-2021. Pandemic Wave 3 included admissions between 18-05-2021 and 30-11-2021 and discharged prior to 28-12-2021. The comparator period included admissions between 01-03-2018 and 30-11-2019 and discharged prior to 28-12-2019.

Median and interquartile range were calculated for continuous variables, and frequencies and percentages presented for categorical variables. Missing data were reported where relevant. Data were stratified according to admission period (comparator or pandemic), and COVID-19 admission status. Differences between groups were assessed for significance using Mann Whitney-U tests (Wilcoxon Rank Sum tests) for continuous variables, and Pearson chi-square tests for categorical variables. Except where specified, a threshold for significance of $p<0.05$ was used throughout.

Detailed data on source of infection was not available. As a proxy for this, univariate analysis was undertaken on the subgroup of patients who got an ICU-acquired infection: the percentage of patients with a) a CVC in situ, or b) undergoing intubation, on the date of onset of infection or at any point in the two calendar days prior, was calculated in each admission period, and by COVID-19 admission status.

The 20 microorganisms most frequently isolated within each group, and rates of microorganism incidence per 1000 patient days were described, with unadjusted rate ratios calculated for comparisons between groups.

## Incidence Rate Analyses

BSI incidence rates were calculated per 1000 patient days. Patient days were calculated from length of ICU stay, with admission treated as day one. Rates were calculated by admission period and COVID-19 admission status. Unadjusted incidence rate ratios (RR) were calculated to compare incidence between a) the pandemic and comparator periods; b) non-COVID-19 admissions during the pandemic and the comparator period; and c) COVID-19 and non-COVID-19 admissions during the pandemic.

## Statistical Modelling

Cox regression was undertaken on a subset of cases where data were available across all variables of interest (complete case analysis). This resulted in inclusion of 19,871 cases from the comparator period and 17,972 from the pandemic period. Time-to-event was calculated to correspond with the definition of ICU-acquired BSI and was therefore defined as the number of days from day three of admission to the first of the following events: onset of infection, death, or discharge plus two days. Data were censored at the date of event, and only the first BSI of an admission was included in the model.

**Model cohorts:** modelling was undertaken in two cohorts, to explore the primary variables of interest: cohort one ("non-COVID-19 cohort") comprised all cases during the comparator period and non-COVID-19 cases during the pandemic period, with the primary risk factor of interest being time-period of ICU stay; cohort two ("pandemic cohort") comprised of all the pandemic cohort cases, and the primary variable of interest was COVID-19 admission status.

**Model endpoints:** it was recognised that death was a competing event to infection, therefore a competing risk approach was used to model against two endpoints[10]: a) the primary endpoint of BSI, against those without BSI, and b) the competing outcome of death with no BSI, against those with BSI or discharged alive without BSI. The BSI endpoint models included patients who died, censored at date of death, and the mortality endpoint models included cases who contracted a BSI, censored at date of infection. Model cohorts and endpoints are summarised in figure 1.

**[Insert Figure 1.]**

Competing risk cox regression models were undertaken for each cohort and endpoint to produce Cause-Specific Hazard Ratios (HRs) for risk factors of interest. Cumulative incidence functions (CIF) were plotted to illustrate the probability of competing events across survival time for the primary risk factors of interest (time-period, or COVID-19 admission status). CIFs were unadjusted for additional risk factors included in the modelling.

Variables of interest were selected for inclusion into the models based on availability of data, evidence from wider literature, and preliminary analysis exploring relationships with the outcome of interest (BSI or mortality) and the primary variables of interest (time-period, or COVID-19 admission status). Any change in the proportional distribution of BSI or mortality in the levels of each variable of interest between time-period or COVID-19 warranted inclusion in the initial models. Models were then refined to prevent violations of proportional hazards and improve fit utilising model concordance score. The final variables included in the models were: time-period, COVID-19 admission status, age group, sex, APACHE II score, Charlson score, admission type, antimicrobial use in the two days before and after admission, transfer between ICUs during stay, any CVC use, and any intubation.

Interactions between the primary variables of interest (time-period or COVID-19 admission status) and each of the covariates were tested, along with: Charlson score and age group; pandemic wave with each of sex, age group, Charlson score, APACHE II score, any CVC use, and any intubation use; and unit transfer with each of Charlson score, any CVC use, any intubation use, and age group. Interaction terms were included if they were significant at the level of $p<0.01$. Variables and models were assessed for violation of proportional hazard assumptions, and models were stratified to overcome such violations. The final models were adjusted for these covariates; however, inference cannot be carried out on stratification variables and thus they do not appear in model output tables.

Primary models were built against the BSI endpoint (Models 1A and 2A), with the two secondary models for the mortality endpoint (Models 1B and 2B) including the same variables and stratification to allow better comparison of HRs across endpoints within each model cohort.

All analyses were completed in R version 3.6.1.[11]

## Ethical Approval

This study was undertaken by ARHAI Scotland, National Services Scotland (NSS), as part of its duty to monitor and investigate healthcare associated infections. This study is classified as health surveillance under the UK Policy Framework for Health and Social Care Research set out by the NHS Health Research Authority, and thus ethical review is not required.[12] Individual patient consent is not required for ARHAI Scotland to process personal data to conduct specific statutory tasks within the public interest, as set out in NSS ’s Data Protection Notice.[13] Linkage of existing datasets was approved by Public Health Scotland via a Data Release Linkage Form.

# Results

A total 38,081 admission episodes for patients aged 16 or over who spent three or more calendar days in ICU, were included in the study: 17,982 in the pandemic period and 20,099 in the comparator period (Figure 1).

A total of 1397 BSIs were included, of which 1238 were first infections. In the comparator period, 2.2% (n=452) of admissions had at least one BSI. In the pandemic period 4.4% (n=786) of admissions had at least one BSI; 14.3% (n=364) of COVID admissions and 2.7% (n=422) of non-COVID admissions.

Of the 1397 BSIs, 130 (9.3%) were polymicrobial (including two or more different species isolated on the infection date). 8.3% (41/494) of BSIs in the comparator period, and 9.9% (89/903) in the pandemic period were polymicrobial. During the pandemic period 10.7% (47/440) of BSIs in COVID admissions and 9.1% (42/ 463) of BSIs in non-COVID-19 admissions were polymicrobial.

## Descriptive Results

Table 1 describes the patient populations in the pandemic and comparator groups. Length of ICU stay was higher in the pandemic period than the comparator period (median 5 and 4 days, respectively), and higher in COVID-19 than non-COVID-19 admissions during the pandemic (median 10 and 4 days, respectively). Similarly, median days to BSI were higher in the pandemic period than the comparator period (median 10 and 7 days respectively), and higher in COVID-19 than non-COVID-19 admissions (median 11 and 8 respectively).

Differences in proportions were seen across a greater number of patient characteristics when comparing COVID-19 and non-COVID-19 admissions during the pandemic, than when comparing non-COVID-19 admissions during the pandemic with the comparator population. For instance, there was a higher proportion of males in COVID-19 admissions than non-COVID-19 admissions (65.5% compared to 60.5%). Similarly, when compared to the non-COVID-19 admissions during the pandemic, the COVID-19 group had lower Charlson scores (54.3% compared to 35.2% with a score of '0'; and 11.9% compared to 26.3% with a score ≥3), a higher proportion of medical as opposed to surgical admissions (95.3% of COVID-19 admission were medical, compared to 44.7% of non-COVID-19 admissions), and higher proportions of patients with any intubation during their stay (65.1% compared to 57.8%). Only 64.9% of COVID-19 admissions were discharged alive from ICU compared to 90.0% of non-COVID-19 admissions during the pandemic period.

**[Insert Table 1.]**

Table 2 describes the percentage of patients with an ICU-acquired BSI who had a) a CVC in situ, or b) intubation on the date of onset of infection, or at any point in the two calendar days prior. The percentage of those with a CVC in situ during the pandemic period was significantly higher than in the comparator period (91.1% compared to 84.5%), and significantly higher in COVID-19 admissions than in non-COVID-19 admissions (97.5% compared to 85.5%). This pattern was also seen in those patients intubated in the two calendar days prior to BSI: 83.3% of those in the pandemic compared to 65.9% of those in the comparator period were intubated; within the pandemic period this rose to 96.4% of COVID-19 admissions, compared to 72.0% of non-COVID-19 admissions. However, when comparing non-COVID-19 admissions during the pandemic to patients in the comparator period, there were no statistically significant differences in the percentages of those with a CVC in situ or those intubated on the date of onset of infection or in the two days prior.

**[Insert Table 2.]**

## Microorganism Results

From 1397 BSIs, 1545 microorganisms were isolated, of which 278 (18.0%) came from polymicrobial infections. 16.3% (88/541) of isolates in the comparator period were polymicrobial. In the pandemic period 18.9% (190/1004) overall, 20.8% (103/496) in COVID-19 admissions, and 17.1% (87/508) in non-COVID-19 admissions were from polymicrobial infections.

The most frequently reported microorganism isolated from ICU-acquired BSI in the pandemic cohort was *Staphylococcus aureus* (14.5% overall; 15.9% in COVID-19 admissions, and 13.2% in non-COVID-19 admissions), followed by *Staphylococcus epidermidis* (10.1% overall; 9.3% in COVID-19 admissions, and 10.8% in non-COVID-19 admissions). However, in the comparator period, *Escherichia coli* (13.9%) was most frequently reported, followed by *S. aureus* (11.5%) (Table S1, Supplemental Material). There were few significant differences in the percentages of microorganisms seen in the comparator period and pandemic groups. *E. coli* was an exception, accounting for a lower proportion of isolates in the pandemic than in the comparator period (7.9% and 13.9% respectively, p<0.001).

The incidence of *S. aureus* isolated from ICU-acquired BSI per 1000 patient days was significantly higher in the pandemic period compared to the pre-pandemic comparator (1.00 and 0.46 per 1000 patient days, respectively, unadjusted incidence rate ratio (RR) 2.19, 95% Confidence Interval (CI) 1.63-2.95). However, this did not hold true when comparing only non-COVID-19 admissions during the pandemic to the comparator group (rates of 0.63 and 0.46, respectively, unadjusted RR 1.38 (95% CI 0.98-1.95)). COVID-19 admissions had a significantly higher rate of *S. aureus* BSI than non-COVID-19 admissions during the pandemic (1.98 and 0.63 per 1000 patient days, respectively, unadjusted RR 3.14 (95% CI 2.27-4.35)). This same pattern of significance repeated over a number of microorganisms, including *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Staphylococcus hominis,* and *Streptococcus pneumoniae* (Table S2, Supplemental Material).

*E. coli* incidence per 1000 patient days was not significantly different between the pandemic and pre-pandemic periods, however, COVID-19 admissions in the pandemic had a significantly higher rate than non-COVID-19 admissions (rates of 0.90 and 0.40, respectively, unadjusted RR 2.23 (95% CI 1.43-3.47)).

No microorganisms were found to have a significantly higher incidence per 1000 patient days in the comparator period than either in the overall pandemic period, or in non-COVID-19 admissions during the pandemic. Care must be taken in interpretation of these due to small sample sizes in some of the microorganisms isolated, and the unadjusted nature of the RR doesn’t account for the differences in the population seen in each time-period.

## Incidence Rate Results

The incidence of BSI was higher during the pandemic period than the comparator period (unadjusted RR 1.70, 95% Confidence Interval (CI) 1.52-1.90), with COVID-19 admissions having a higher rate than non-COVID-19 admissions (unadjusted RR 2.53, 95% CI 2.22-2.89). Additionally, non-COVID-19 admissions during the pandemic had a higher incidence of BSI than admissions during the comparator period (unadjusted RR 1.20, 95% CI 1.06-1.36) (Table 3).

**[Insert Table 3.]**

## Modelling Results

Two hundred and thirty-eight admissions were excluded in the complete case multivariable analysis. The model dataset therefore included 2550 COVID-19 admissions and 15,422 non-COVID-19 admissions in the pandemic period, and 19,871 admissions in the comparator period. The two model cohorts consisted of 35,293 admissions in the non-COVID-19 cohort (comparator plus non-COVID-19 pandemic admissions), and 17,972 in the pandemic cohort (Figure 1).

## Cox Regression and CIF Results

Admission to the ICU during pandemic wave 1 and wave 2a significantly increased the hazard of BSI when compared to admission during the comparator period (HR 1.27 95% CI 1.02-1.59 and HR 1.39 95% CI 1.14-1.70 for wave 1 and wave 2a, respectively). Admission during wave 2b or 3 had no significant effect (Table 4, Model 1A). Figure 2(a) shows a higher probability at each time point of developing a BSI in patients admitted during the pandemic overall compared to the comparator period. The relationship with probability of death at any given time point between the comparator and pandemic period is less clear (Figure 2(a)). When tested, pandemic wave did not significantly affect the hazard of the competing outcome of death (Table 4, Model 1B). Additional variables that increased the HR of BSI included male sex, Charlson score ≥3, APACHE II score >20, intubation, and CVC use. Those with a transfer between ICUs during their stay had a reduced HR for both BSI and the competing outcome of death. Models 1A and 1B were stratified by admission type and antimicrobial use due to their violation of proportional hazard assumptions, indicating that their HRs varied according to survival time.

**[Insert Figure 2.]**

In the pandemic cohort, figure 2(b) shows a higher probability at each time point of developing a BSI or dying in patients admitted with COVID-19 than in those admitted without COVID-19. In the models (Table 5, models 2A and 2B) COVID-19 admission did significantly increase the hazard of the competing outcome of death (HR 2.26 95% CI 1.77-2.88). COVID-19 admission did not significantly increase the HR for BSI, when other variables were adjusted for. However, an interaction between COVID-19 on admission and intubation significantly increased the HR of BSI (HR 4.64 95% CI 2.07-10.4) and reduced the HR of mortality (HR 0.42 95% CI 0.33-0.55). This reflects what is seen in the CIF plotted in figure 2(b), where for those with COVID-19 the difference between competing outcomes in the first 10 days is the smallest. Male sex and CVC use significantly increased the HRs of BSI, whereas of these, only CVC use also significantly increased the hazard of the competing outcome of death. Other variable groups raising the HRs in the mortality model included intubation, higher age group, Charlson score ≥3, and higher APACHE II score. Due to violations of the proportional hazards assumption, Models 2A and 2B were stratified by time-period, admission type, antimicrobial use, and transfer between ICUs.

**[Insert Table 4.]**

**[Insert Table 5.]**

# Discussion

The aim of this study was to explore changing rates in ICU-acquired BSI during the COVID-19 pandemic in comparison to a period prior to the pandemic, and subsequently to investigate risk factors and population differences that may influence these rates.

*S. aureus* was the most frequently reported microorganism identified in blood during the pandemic, in comparison with *E. coli* in the pre-pandemic period. The incidence of *S. aureus* ICU-acquired BSI was significantly higher during the pandemic period compared to pre-pandemic, however *E. coli* incidence was not significantly different between these two periods.

Our unadjusted incidence rate analyses confirm previous studies' findings that patients who were admitted to ICUs during the pandemic, particularly those admitted with COVID-19, had higher rates of BSI.[3,4,14-16]

Multivariate-adjusted modelling of pandemic wave on ICU patients without COVID-19 demonstrated that admission to ICU earlier in the pandemic during waves 1 and 2a significantly increased the risk of BSI in comparison to the pre-pandemic period (HR 1.27 95% CI 1.02-1.59, and HR 1.39 95% CI 1.14-1.70 respectively, Table 4), whereas admission during waves 2b and 3 did not. When adjustment for potential confounders was made during modelling, admission with COVID-19 was not a significant risk factor for BSI. However, an interaction with intubation suggests that COVID-19 patients with this clinical intervention may have had a greater risk of BSI (HR 4.64 95% CI 2.07-10.4, Table 5). Multivariate-adjusted modelling for confounders and descriptive analysis demonstrates that incidence rates cannot be interpreted without the consideration of additional demographic and clinical risk factors.

## Exploring our Findings

The changing microbiology observed in ICU-acquired BSIs in Scotland between 2019 and 2020 is consistent with previous internal ARHAI Scotland reports.[17,18] Our results contrast with those of UKHSA, where the percentage of CCU-acquired BSIs attributable to both *S. aureus* and *E. coli* in England fell between 2019-2020 data and 2020-2021 data.[19]

Given the lack of information available on source of BSI, it is hard to ascertain the reasons behind changing microbiology, and we cannot rule out blood culture contamination. However, there were higher proportions of patients with CVC or intubation during their stay in the pandemic than in the pre-pandemic period. Moreover, in the pandemic a greater percentage of those who acquired a BSI had a CVC in situ or were intubated in the two days prior to infection, or on the date of infection, than in the pre-pandemic. Vascular access devices were the most common entry points for *S. aureus* bacteraemias in Scotland in 2019 and 2020, with 26.9% and 23.1% respectively.[20,21] Additionally, evidence from other countries indicates that rates of device associated infections (in particular central line associated BSIs (CLABSIs) and ventilator associated pneumonias (VAPs)) increased during the pandemic.[16,19,22-24] Notably, Singapore appears to be an exception to this: researchers found healthcare-associated respiratory-viral infections other than SARS-CoV-2, MRSA rates, and central line associated BSIs all declined. Rates of other HAIs remained stable. When looking at ICUs specifically, rates of CLABSI, CAUTI and VAP all remained stable.[25]

This study highlights changes in the patient case-mix in the ICU during the COVID-19 pandemic, and interpretations of rates of BSI must be considered with this in mind. Before the pandemic, ICU admissions included more elective surgery patients, with a reduction during the pandemic due to elective surgeries being postponed or cancelled to provide capacity for COVID-19 patients.[26]

This study has indicated that the risk of BSI in patients without COVID-19 differed across pandemic waves and is likely to reflect the multifactorial changes over the pandemic to the ICU environment, practices, and staffing.[1,8] These changes included the use of makeshift ICU departments to meet the demands during the pandemic; staffing pressures from increased requirements in handling and proning of COVID-19 patients; more non-ICU and agency staff on the units; and sessional use of personal protective equipment (PPE), including long-sleeved gowns.[1,27] Guidance was changed in Scotland in late 2020 and early 2021 and the sessional use of PPE other than fluid resistant surgical masks or FFP3 masks was no longer supported.[28,29] Sessional use of PPE may have contributed to the increased risk of BSI earlier in the pandemic through a reduction in hand hygiene practices due to sessional gloves and long-sleeved aprons being worn. Additionally, national baseline capacity of intensive care beds was often exceeded early in the pandemic and during early 2021. Care was often delivered in areas of the hospital re-purposed to provide intensive care, resulting in additional stress on staffing.[26]

Pandemic waves were also generally representative of dominant COVID-19 variants and associated severity, as well as treatments and changing levels of individual immunity with vaccination and past infection history over the period. Differences in BSI incidence between pandemic waves were reported elsewhere in the UK – UKHSA reported that in adult critical care units (CCU), the rate of BSIs rose sharply during the early stages of the pandemic (from 3.6 to 6.3 CCU-acquired BSIs per 1,000 bed-days over 2 nights), but then returned to pre-pandemic levels.[19]

Our multivariate modelling results showed that admission with COVID-19 was not a significant risk factor for BSI when adjusting for demographic and clinical factors, which contradicts previous literature where COVID-19 was found to be a significant risk factor.[14,15] However, the interaction with intubation increased the HR for BSI in those admitted with COVID-19 to a larger extent than it increased the HR in those admitted without COVID-19 (HR of the interaction 4.64 95% CI 2.07-10.4). Intubation as a risk factor for BSI in COVID-19 patients is echoed in the literature.[30] Intubation was more protective against death in the COVID-19 admissions than in the non-COVID-19 admissions (HR of interaction 0.42 95% CI 0.33-0.55). In COVID-19 admissions, intubation was therefore more of a risk for BSI, but also more protective against death than in non-COVID-19 admissions. Furthermore, COVID-19 admission status was significant in increasing the hazard of the competing outcome of death (HR 2.26 95% CI 1.77-2.88), which impacts on the population remaining at risk of BSI. Finally, care should be taken with the interpretation of COVID-19 as a binary risk factor as it does not consider the importance of disease severity.[31] This may be compounded by testing policies which result in the inclusion of asymptomatic cases in the COVID-19 admissions group.[32]

Having a CVC in situ at any point up until censor date was particularly notable in increasing the hazard of contracting a BSI both in the non-COVID-19 cohort (HR 3.14 95% CI 2.33-4.23)) and in the pandemic cohort (HR 3.58 95% CI 2.34-5.46). CVC use has consistently been reported as the main associated risk factor for BSI during the pandemic in the UK[5] and USA[7], and specifically in COVID-19 patients.[4] Our univariate analysis of device use, discussed above, is consistent with this. However, the similarity of the magnitude of effect across cohorts suggests practices in CVC in situ may not be a driving factor for the differences in overall BSI incidence.

Older age, higher Charlson co-morbidity score, higher APACHE II score, and device use, were significantly associated with increased hazard of death in both the non-COVID-19 and pandemic cohorts. The HR of BSI appears to decline with older age group in both cohorts. However, as the risk of mortality increased with age, this suggests the underlying population is being censored in the older age group prior to opportunity to contract a BSI. Notably, those intubated had a higher HR than those with a CVC against the mortality endpoint, whereas the opposite was seen against the BSI endpoint in both cohort models. These comparisons highlight the importance of considering mortality as a competing outcome in analyses of ICU-acquired infections, where increasing risk of death may censor patients from the population at risk of BSI.

Transfer between ICUs during the stay was the only covariate to have a protective effect on both BSI and the competing outcome of mortality in the non-COVID-19 cohort. Those with a transfer constituted just over 5% of the model cohort, but due to the nature of transfers between ICUs being counted as one continuous ICU stay, longer length of stay may allow for the possibility of more transfers, which may lead to an incidental protective effect on the outcome. Similarly, patients being well enough to be transferred could offer a plausible explanation of protective effects. After investigation of all model variables, no significant confounder was found in relation to transfer between ICUs.

## Generalisability

This paper describes and analyses health surveillance data from all ICUs in NHS Scotland and therefore provides an opportunity to describe BSI in an ICU population in a small, high income country. The findings are intended to contribute to the wider evidence base and our results do reflect trends seen in other countries. Caution should be applied when comparing results to other countries due to differences such as IPC practices, resource availability, patient populations, and pandemic response. However, challenges in Scottish ICUs during the pandemic with the ICU environment, sessional use of PPE, and over-capacity were likely to have been experienced in other countries, therefore the findings have wider relevance. The ICU environment, the availability of ICU-trained staff, and adherence to IPC practices are fundamental principles that help reduce the risk of HAIs, and are generalisable to all ICUs.

## Strengths and Limitations

A major strength of this study is the consideration of time to infection, and inclusion of mortality as a competing outcome with ICU-acquired infection.[33-35] Using cox regression with a competing risk approach, rather than logistic regression, prevents loss of information around time to event, and length of stay.

Our large national dataset enabled a study of all ICUs across Scotland. Linkage of three datasets allowed us to explore a wider variety of risk factors, however we experienced issues around missing data. In our descriptive analyses we included a ‘missing’ category for variables where applicable, which allowed investigation of bias in these groups. In our multivariate models we were only able to include patients where all relevant variables were complete.

Scottish ICUs undertake mandatory surveillance of BSIs, catheter-related infections, and both ventilator associated and non-ventilator associated pneumonias.[36] Surveillance of HAIs in ICUs is not mandatory in all countries, including in the UK. Mandatory ICU surveillance was paused in Scotland during the COVID-19 pandemic, which led to key variables being unavailable. Lack of data on source of infection restricted investigation into whether BSIs were true infections, rather than due to contamination. This was of particular concern due the predominance of *S. aureus* isolated during the pandemic period, and lack of information on clinical signs and symptoms of true infection. However, an increase in blood culture contaminants remains important – other studies have reported an increase during the pandemic, including in ICUs.[37-40] Analyses were also constrained by a lack of data on clinical course and deterioration, shock, and vasopressor use. Nor was data available on the healthcare built environment, IPC procedures, and patient characteristics such as vaccination status, ethnicity and body mass index (BMI) – which has been found to be independently associated with nosocomial infection in COVID-19 ICU patients.[41] Additionally, we were unable to look at prescribing data; evidence suggests treatments for COVID-19 may significantly increase the hazard of developing BSI.[30,42-44]

Multivariable modelling demonstrated the importance of accounting for the complex multifactorial influences of demographic and clinical risk factors when interpreting rates analysis. However, the need to include the same variables in both models led to some violation of proportional hazards in the secondary mortality models. Investigation of APACHE II score violations in both models 1B and 2B revealed clinically anticipated higher initial probabilities of death post-admission in the highest scoring group. Additionally, while stratification of models to overcome proportional hazard violations improved model validity, it limited the interpretation of these variables. HRs for pandemic wave could only be produced for the non-COVID-19 cohort (models 1A and 1B), as the pandemic cohort models (2A and 2B) were stratified by this variable. Our ability to make inferences regarding the impact of pandemic wave in COVID-19 patients is therefore constrained.

Finally, some of the binary variables included in the regression models – any CVC, intubation, or transfer between ICUs prior to censor date – could be explored further as time-dependent covariates. Analysing the data at the daily level may provide further insight into source of infection, and warrants further investigation.

## Implications

Our findings emphasize the importance of device management and IPC, and consideration of unintended consequences when initiating emergency controls such as sessional use of PPE. NHS Scotland provides guidance on IPC in the National Infection Prevention and Control Manual, and has published bundles on inserting and maintaining CVCs, and on prevention of ventilator associated pneumonia in those patients who are intubated.[45-47] Additionally, the ECDC sets out key items that should be monitored to ensure good IPC practice in ICUs, including around intubation and CVC use.[48] Unfortunately, there are no data on adherence to these guidelines in Scottish ICUs during the pandemic.

Similarly, we recommend adherence to the Health and Care (Staffing) (Scotland) Act 2019, which sets out minimum levels of staffing to enable safe and high quality care[49], and to Health Building Note 04-02 (HBN 04-02) for Critical Care Units[50], which sets out design and safety specifications for critical care facilities. We know that in Scottish ICUs during the pandemic, supplementation with non-ICU staff and the use of non-compliant areas not designed to meet HBN 04-02, was required.[1]

Preparedness for future pandemics should consider the risks and benefits of the use of sessional PPE, particularly long-sleeve gowns, in high consequence infectious diseases.[51] The higher BSI rates earlier in the pandemic period and correlation with sessional PPE practice highlights the careful balance required for prioritising safety of health care workers whilst minimising the risk of HAI for patients.

Our study emphasizes the importance of mandatory surveillance of HAIs in ICUs. Additionally, we highlight the necessity of including mortality as a competing outcome in populations where risk of death is high. Our study was restricted to the pandemic period up to the end of 2021, to allow comparisons between COVID-19 and non-COVID-19 ICU admissions prior to the predominance of the Omicron variant. The epidemiology of COVID-19 changed with the Omicron variant, and COVID-19 became coincidental to ICU admission rather than the reason for admission in the majority of cases.[26,52,53] Future studies should include an additional comparator period from more recent years to improve understanding of our findings, but must consider the changing context and epidemiology of COVID-19. Finally, where data is available, analyses should include key variables such as source of infection, COVID-19 vaccination status, BMI, ethnicity, IPC procedures, environmental variables, and prescribing data.

# Conclusion

This is the first study to investigate changing rates of ICU-acquired BSI in Scotland prior to and during the pandemic, and to model the underlying factors influencing these rates. To our knowledge this is the only study that analyses ICU-acquired BSIs during the pandemic that considers mortality as a competing outcome.

While incidence rates of ICU-acquired BSI are higher in the pandemic period than the pre-pandemic period, and in COVID-19 admissions, this is likely to be driven by multifactorial relationships between demographic and clinical factors within these populations. Caution should be taken when analysing the pandemic period as a whole, as our results indicate ICU-acquired BSI variation across pandemic waves in admissions of patients without COVID-19, likely reflecting changes over time in patient admissions, disease severity, IPC procedures and adherence, staffing pressures, vaccination, and available treatments. Future research should investigate these changes across time periods and admission groups to enable a deeper understanding of BSI acquisition hazards, and include a post-pandemic comparator period to understand how rates and hazards have shifted over more recent years.

Finally, we recommend regular surveillance of HAIs in ICUs, and adherence to guidelines around IPC practices, staffing levels, and unit design. Future pandemic preparedness should consider these elements, whilst considering the risks of practices such as sessional use of PPE.

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**[Insert Appendix A. Variable Names and Definitions]**

***Table 1. Characteristics of population broken down by time-period and COVID-19 admission status***

| Variable | Sub-group | Comparator | Pandemic | | | Statistical tests | | |
|---|---|---|---|---|---|---|---|---|
| | | | **All** | **COVID-19** | **Non-COVID-19** | **Pandemic (all)/ Comparator** | **Pandemic (non-COVID-19)/ Comparator** | **Pandemic COVID-19/ non-COVID-19** |
| Admissions and episodes | | n | | | | | | |
| Total admissions (continuous ICU stays) | All | 20,099 | 17,982 | 2,553 | 15,429 | - | - | - |
| Total BSIs | All | 494 | 903 | 440 | 463 | - | - | - |
| Admissions with any BSI (number of first BSIs) | All | 452 (2.2%) | 786 (4.4%) | 364 (14.3%) | 422 (2.7%) | - | - | - |
| Mortality Outcome | | % (n) | | | | | | |
| Mortality status on ICU discharge | Alive | 89.9% (18,063) | 86.5% (15,549) | 64.9% (1658) | 90.0% (13,891) | - | - | - |
| | Died | 10.1% (2032) | 13.5% (2429) | 35.0% (893) | 10.0% (1536) | - | - | - |
| | Missing | 0.0% (4) | 0.0% (4) | 0.1% (2) | 0.0% (2) | - | - | - |
| Characteristics of population: Continuous variables | | Median (IQR) | | | | Mann Whitney-U test (Wilcoxon rank-sum) | | |
| Median days to BSI (from date of admission to ICU unit) | All | 7 (5-12) | 10 (6-16) | 11 (8-17) | 8 (6-14) | p<0.001 | p=0.025 | p<0.001 |
| Length of ICU Stay (days) | All | 4 (3-7) | 5 (3-8) | 10 (6-20) | 4 (3-7) | p<0.001 | p=0.112 | p<0.001 |
| Characteristics of population: categorical variables | | % (n) | | | | Proportion tests (Pearson's chi-square) | | |
| Age Group | 16-49 | 23.5% (4717) | 24.8% (4458) | 24.2% (619) | 24.9% (3839) | p<0.001 | p<0.001 | p<0.001 |
| | 50-59 | 19.2% (3859) | 21.0% (3775) | 27.0% (690) | 20.0% (3085) | | | |
| | 60-69 | 24.9% (5004) | 26.2% (4712) | 31.4% (801) | 25.3% (3911) | | | |
| | 70+ | 32.4% (6519) | 28.0% (5037) | 17.4% (443) | 29.8% (4594) | | | |

| Variable | Sub-group | Comparator | Pandemic | | | Statistical tests | | |
|---|---|---|---|---|---|---|---|---|
| | | | All | COVID-19 | Non-COVID-19 | Pandemic (all)/ Comparator | Pandemic (non-COVID-19)/ Comparator | Pandemic COVID-19/ non-COVID-19 |
| Sex | Female | 40.6% (8157) | 38.8% (6977) | 34.5% (881) | 39.5% (6096) | p<0.001 | p=0.042 | p<0.001 |
| | Male | 59.4% (11,942) | 61.2% (11,005) | 65.5% (1672) | 60.5% (9333) | | | |
| Time-Period | Pre-pandemic (comparator) | 100.0% (20,099) | - | - | - | - | - | - |
| | Pandemic Wave 1 | - | 20.9% (3760) | 18.3% (467) | 21.3% (3293) | - | - | p<0.001 |
| | Pandemic Wave 2a | - | 23.8% (4287) | 19.3% (493) | 24.6% (3794) | - | - | |
| | Pandemic Wave 2b | - | 22.5% (4042) | 28.5% (728) | 21.5% (3314) | - | - | |
| | Pandemic Wave 3 | - | 32.8% (5893) | 33.9% (865) | 32.6% (5028) | - | - | |
| Patient Origin | Community | 24.0% (4816) | 26.9% (4843) | 28.6% (729) | 26.7% (4114) | p<0.001 | p<0.001 | p<0.001 |
| | Hospital Area | 76.0% (15,283) | 73.1% (13,139) | 71.4% (1824) | 73.3% (11,315) | | | |
| Trauma admission | No | 93.5% (18,791) | 95.0% (17,078) | 99.3% (2535) | 94.3% (14,543) | p<0.051 | p<0.303 | p<0.001 |
| | Yes | 5.4% (1085) | 5.0% (900) | 0.7% (18) | 5.7% (882) | | | |
| | Missing | 1.1% (223) | 0.0% (4) | - | 0.0% (4) | - | - | - |
| Charlson Score | 0 | 34.0% (6846) | 37.9% (6813) | 54.3% (1387) | 35.2% (5426) | p<0.001 | p<0.004 | p<0.001 |
| | 1-2 | 37.9% (7624) | 37.9% (6813) | 33.8% (862) | 38.6% (5951) | | | |
| | ≥3 | 28.0% (5629) | 24.2% (4356) | 11.9% (304) | 26.3% (4052) | | | |
| Admission Type | Medical | 43.1% (8667) | 51.9% (9334) | 95.3% (2432) | 44.7% (6902) | p<0.001 | p<0.001 | p<0.001 |

| Variable | Sub-group | Comparator | Pandemic | | | Statistical tests | | |
|---|---|---|---|---|---|---|---|---|
| | | | All | COVID-19 | Non-COVID-19 | Pandemic (all)/ Comparator | Pandemic (non-COVID-19)/ Comparator | Pandemic COVID-19/ non-COVID-19 |
| | Surgical (Elective) | 31.2% (6266) | 23.4% (4199) | 0.6% (15) | 27.1% (4184) | | | |
| | Surgical (Emergency) | 24.6% (4942) | 24.7% (4443) | 4.1% (105) | 28.1% (4338) | | | |
| | Surgical (Type Unknown) | 0.0% (1) | 0.0% (2) | 0.0% (1) | 0.0% (1) | | | |
| | Missing | 1.1% (223) | 0.0% (4) | - | 0.0% (4) | - | - | - |
| Antimicrobial use in 48 hours before and/or after admission | No | 22.5% (4515) | 20.7% (3724) | 17.2% (440) | 21.3% (3284) | p<0.001 | p<0.001 | p<0.001 |
| | Yes | 76.4% (15,361) | 79.3% (14,254) | 82.8% (2113) | 78.7% (12,141) | | | |
| | Missing | 1.1% (223) | 0.0% (4) | - | 0.0% (4) | - | - | - |
| APACHE II score | 0-10 | 40.7% (8175) | 37.3% (6701) | 24.0% (613) | 39.5% (6088) | p<0.001 | P=0.012 | p<0.001 |
| | 11-20 | 41.3% (8301) | 44.2% (7944) | 60.8% (1553) | 41.4% (6391) | | | |
| | >20 | 18.0% (3623) | 18.6% (3337) | 15.2% (387) | 19.1% (2950) | | | |
| Any CVC* | No | 31.7% (6369) | 28.0% (5034) | 29.9% (764) | 27.7% (4270) | p<0.001 | p<0.001 | p=0.020 |
| | Yes | 68.3% (13,730) | 72.0% (12,948) | 70.1% (1789) | 72.3% (11,159) | | | |
| Any intubation* | No | 44.6% (8956) | 41.2% (7407) | 35.0% (893) | 42.2% (6514) | p<0.001 | p<0.001 | p<0.001 |
| | Yes | 55.4% (11,143) | 58.8% (10,575) | 65.0% (1660) | 57.8% (8915) | | | |
| Transfer between ICUs during stay* | No | 94.8% (19,029) | 94.1% (16,901) | 94.9% (2423) | 94.0% (14,478) | p=0.004 | p=0.001 | p=0.066 |
| | Yes | 5.2% (1050) | 5.9% (1061) | 5.1% (130) | 6.0% (931) | | | |

*May have occurred at any time point during the length of ICU stay and is censored at date of BSI or death whichever was prior.

*Table 2. Percentage of patients with an ICU-acquired infection with device use prior to onset of infection*

| | Comparator admissions | Pandemic admissions | | | Statistical tests | | |
|---|---|---|---|---|---|---|---|
| | **All** | **All** | **COVID-19** | **non-COVID-19** | **Pandemic (all)/ Comparator** | **Pandemic non-COVID-19/ Comparator** | **Pandemic COVID-19/Pandemic non-COVID-19** |
| Percentage of patients with CVC in situ on date of onset of infection, or in 2 days prior | 84.5% (382) | 91.1% (716) | 97.5% (355) | 85.5% (361) | P<0.001 | P=0.740 | P<0.001 |
| Percentage of patients intubated on date of onset of infection, or in 2 days prior | 65.9% (298) | 83.3% (655) | 96.4% (351) | 72.0% (304) | P<0.001 | P=0.061 | P<0.001 |

*Table 3. Rates of ICU BSI per 1000 patient days at risk.*

| | Comparator admissions | Pandemic admissions | | | Unadjusted Rate Ratios (RR) | | |
|---|---|---|---|---|---|---|---|
| | **All** | **All** | **COVID-19** | **non-COVID-19** | **Pandemic (all)/ Comparator** | **Pandemic (non-COVID-19)/ Comparator** | **Pandemic COVID-19/ non-COVID-19** |
| Total patient days (from LOS in ICU) | 136,207 | 146,416 | 39,946 | 106,470 | - | - | - |
| Number of BSIs | 494 | 903 | 440 | 463 | - | - | - |
| BSIs per 1000 patient days at risk (95% CI) | 3.63 (3.31-3.96) | 6.17 (5.77-6.58) | 11.01 (10.01-12.09) | 4.35 (3.96-4.76) | 1.70 (1.52-1.90, p<0.001) | 1.20 (1.06-1.36, p<0.001) | 2.53 (2.22-2.89, p<0.001) |

***Table 4: Regression Output: Non-COVID-19 cohort***

| | | Model 1A: Primary Endpoint (BSI) | | | Model 1B: Competing Endpoint (Mortality) | | |
|---|---|---|---|---|---|---|---|
| **Variable[1]** | **N = 35,293[2]** | **HR[3]** | **95% CI[3]** | **p-value** | **HR[3]** | **95% CI[3]** | **p-value** |
| **Endpoint** | | | | | | | |
| Discharged alive without BSI | 31,075 (88.0%) | | | | | | |
| BSI | 870 (2.5%) | | | | | | |
| Death with no BSI | 3,348 (9.5%) | | | | | | |
| **Time-Period** | | | | | | | |
| Comparator | 19,871 (56.3%) | — | — | | — | — | |
| Pandemic Wave 1 | 3,289 (9.3%) | 1.27 | 1.02, 1.59 | 0.032 | 0.92 | 0.82, 1.04 | 0.195 |
| Pandemic Wave 2a | 3,792 (10.7%) | 1.39 | 1.14, 1.70 | 0.001 | 0.90 | 0.80, 1.01 | 0.082 |
| Pandemic Wave 2b | 3,314 (9.4%) | 0.93 | 0.73, 1.19 | 0.588 | 0.98 | 0.87, 1.10 | 0.733 |
| Pandemic Wave 3 | 5,027 (14.2%) | 1.05 | 0.86, 1.27 | 0.655 | 0.93 | 0.84, 1.03 | 0.159 |
| **Sex** | | | | | | | |
| Female | 14,142 (40.1%) | — | — | | — | — | |
| Male | 21,151 (59.9%) | 1.27 | 1.10, 1.47 | <0.001 | 0.94 | 0.88, 1.01 | 0.107 |
| **Age Group** | | | | | | | |
| 16-49 | 8,523 (24.1%) | — | — | | — | — | |
| 50-59 | 6,909 (19.6%) | 0.92 | 0.77, 1.11 | 0.395 | 1.33 | 1.20, 1.48 | <0.001 |

| | | Model 1A: Primary Endpoint (BSI) | | | Model 1B: Competing Endpoint (Mortality) | | |
|---|---|---|---|---|---|---|---|
| **Variable**[1] | **N = 35,293**[2] | **HR**[3] | **95% CI**[3] | **p-value** | **HR**[3] | **95% CI**[3] | **p-value** |
| 60-69 | 8,846 (25.1%) | 0.81 | 0.67, 0.98 | 0.031 | 1.61 | 1.45, 1.78 | <0.001 |
| 70+ | 11,015 (31.2%) | 0.76 | 0.62, 0.92 | 0.005 | 2.09 | 1.89, 2.31 | <0.001 |
| **Charlson Score** | | | | | | | |
| 0 | 12,206 (34.6%) | — | — | | — | — | |
| 1-2 | 13,507 (38.3%) | 1.21 | 1.04, 1.42 | 0.016 | 0.96 | 0.89, 1.05 | 0.371 |
| ≥3 | 9,580 (27.1%) | 1.09 | 0.90, 1.31 | 0.385 | 1.09 | 1.00, 1.19 | 0.047 |
| **APACHE II Score** | | | | | | | |
| 0-10 | 14,167 (40.1%) | — | — | | — | — | |
| 11-20 | 14,580 (41.3%) | 1.11 | 0.94, 1.33 | 0.222 | 1.12 | 1.00, 1.24 | 0.040 |
| >20 | 6,546 (18.5%) | 1.44 | 1.19, 1.73 | <0.001 | 2.62 | 2.36, 2.90 | <0.001 |
| **Intubated** | | | | | | | |
| No | 15,290 (43.3%) | — | — | | — | — | |
| Yes | 20,003 (56.7%) | 1.19 | 0.98, 1.45 | 0.083 | 2.59 | 2.32, 2.88 | <0.001 |
| **CVC** | | | | | | | |
| No | 10,510 (29.8%) | — | — | | — | — | |
| Yes | 24,783 (70.2%) | 3.14 | 2.33, 4.23 | <0.001 | 1.53 | 1.36, 1.72 | <0.001 |

| | | Model 1A: Primary Endpoint (BSI) | | | Model 1B: Competing Endpoint (Mortality) | | |
|---|---|---|---|---|---|---|---|
| **Variable**[1] | **N = 35,293**[2] | **HR**[3] | **95% CI**[3] | **p-value** | **HR**[3] | **95% CI**[3] | **p-value** |
| **Transfer between ICUs** | | | | | | | |
| No | 33,282 (94.3%) | — | — | | — | — | |
| Yes | 2,011 (5.7%) | 0.77 | 0.62, 0.95 | 0.016 | 0.54 | 0.47, 0.62 | <0.001 |

[1]Models 1A and 1B stratified by admission type and antimicrobial use to correct violations of the proportional hazards assumption
[2]n (%)
[3] HR = Cause-Specific Hazard Ratio, CI = Confidence Interval

***Table 5: Regression Output Pandemic Cohort***

| | | Model 2A: Primary Endpoint (BSI) | | | Model 2B: Competing Endpoint (Mortality) | | |
|---|---|---|---|---|---|---|---|
| **Variable[1]** | **N = 17,972[2]** | **HR[3]** | **95% CI[3]** | **p-value** | **HR[3]** | **95% CI[3]** | **p-value** |
| **Endpoint** | | | | | | | |
| Discharged alive without BSI | 15,054 (83.8%) | | | | | | |
| BSI | 784 (4.4%) | | | | | | |
| Death with no BSI | 2143 (11.9%) | | | | | | |
| **COVID-19 Admission Status** | | | | | | | |
| Non-COVID-19 | 15,422 (85.8%) | — | — | | — | — | |
| COVID-19 | 2,550 (14.2%) | 0.46 | 0.21, 1.02 | 0.057 | 2.26 | 1.77, 2.88 | <0.001 |
| **Sex** | | | | | | | |
| Female | 6,975 (38.8%) | — | — | | — | — | |
| Male | 10,997 (61.2%) | 1.17 | 1.01, 1.37 | 0.042 | 1.00 | 0.91, 1.09 | 0.931 |
| **Age Group** | | | | | | | |
| 16-49 | 4,453 (24.8%) | — | — | | — | — | |
| 50-59 | 3,775 (21.0%) | 0.92 | 0.75, 1.12 | 0.380 | 1.19 | 1.03, 1.37 | 0.016 |
| 60-69 | 4,710 (26.2%) | 0.88 | 0.72, 1.07 | 0.193 | 1.70 | 1.50, 1.94 | <0.001 |
| 70+ | 5,034 (28.0%) | 0.79 | 0.63, 0.99 | 0.044 | 2.28 | 2.00, 2.60 | <0.001 |
| **Charlson Score** | | | | | | | |

| | | Model 2A: Primary Endpoint (BSI) | | | Model 2B: Competing Endpoint (Mortality) | | |
|---|---|---|---|---|---|---|---|
| **Variable[1]** | **N = 17,972[2]** | **HR[3]** | **95% CI[3]** | **p-value** | **HR[3]** | **95% CI[3]** | **p-value** |
| 0 | 6,806 (37.9%) | — | — | | — | — | |
| 1-2 | 6,811 (37.9%) | 1.03 | 0.88, 1.21 | 0.709 | 1.09 | 0.99, 1.21 | 0.071 |
| ≥3 | 4,355 (24.2%) | 0.99 | 0.80, 1.22 | 0.896 | 1.15 | 1.02, 1.29 | 0.020 |
| **APACHE II Score** | | | | | | | |
| 0-10 | 6,695 (37.3%) | — | — | | — | — | |
| 11-20 | 7,941 (44.2%) | 1.09 | 0.90, 1.32 | 0.357 | 1.43 | 1.24, 1.64 | <0.001 |
| >20 | 3,336 (18.6%) | 1.12 | 0.90, 1.39 | 0.315 | 2.86 | 2.48, 3.29 | <0.001 |
| **Intubated** | | | | | | | |
| No | 7,404 (41.2%) | — | — | | — | — | |
| Yes | 10,568 (58.8%) | 1.14 | 0.86, 1.52 | 0.362 | 2.60 | 2.20, 3.07 | <0.001 |
| **CVC** | | | | | | | |
| No | 5,031 (28.0%) | — | — | | — | — | |
| Yes | 12,941 (72.0%) | 3.58 | 2.34, 5.46 | <0.001 | 1.37 | 1.16, 1.63 | <0.001 |
| **COVID-19 Admission Status* Intubated** | | | | | | | |
| COVID-19 * Yes | | 4.64 | 2.07, 10.4 | <0.001 | 0.42 | 0.33, 0.55 | <0.001 |

[1]Models 2A and 2B stratified by time-period, admission type, antimicrobial use, and transfer between ICUs during stay.
[2]n (%)
[3]HR = Cause-Specific Hazard Ratio, CI = Confidence Interval

# Appendix A. Variable Names and Definitions

| Variable | Definition |
|---|---|
| **Admission (CIS)** | Admission to a continuous ICU stay (CIS). Cases where transfers occurred between ICUs consecutively (i.e. from one ICU to another within the same day) were treated as one admission to a continuous ICU stay. Transfers out with an ICU would be considered a discharge, and if the patient was subsequently re-admitted on a different day, this would be considered a separate CIS admission. Recoded into Continuous ICU Stay from ICU Unit admissions data. |
| **Admission Type** | **Medical/Surgical (Elective)/Surgical (Emergency)/Surgical (Type Unknown)**. Derived from variables on nature of admission and nature of surgery. |
| **Age Group** | **16-49/50-59/60-69/70+**. Categorised from continuous age data |
| **Antimicrobial Use** | **No/Yes**. From European Centre for Disease Prevention and Control (ECDC) definition: antibiotic treatment in the 48 hours before ICU admission and/or during the first two days of ICU stay. Includes antibiotic therapy for an infectious event around ICU admission, excluding antifungal and antiviral treatment); does not include antimicrobial prophylaxis, selective digestive decontamination (SDD) or local treatment. |
| **Any CVC*** | **No/Yes**. Presence of a central venous catheter at any time during the ICU stay. |
| **Any Intubation*** | **No/Yes**. Presence of an endotracheal tube or a tracheostomy at any time during the ICU stay. |
| **APACHE II Score** | **0-10/11-20/>20**. Estimation of critical care mortality. Continuous score from clinical team stratified into three categories. Higher score indicative of higher risk of mortality. APACHE II Score excludes pre-sedation Glasgow Coma Score. |
| **Charlson Score** | **0/1-2/≥3.** Charlson score is a weighted score of co-morbidity derived from assigning 'points' to a list of ICD-10 codes for certain co-morbid conditions, calculated using data from the 5 years prior to an individual's ICU admission**.** Categorised from continuous Charlson score of co-morbidity obtained from Scottish Morbidity Record, General/Acute inpatient and day case dataset (SMR01). Maximum score available in this dataset is 24. Diagnoses included in score calculation: heart disease, dementia, pulmonary disease, diseases of connective tissue and the musculoskeletal system, diabetes, hemiplegia/paraplegia, renal disease, HIV/AIDS, liver disease, cancer. |
| **COVID-19 Admission Status** | **COVID-19/Non-COVID-19.** An admission was considered a COVID-19 admission if there was a laboratory confirmation of first COVID-19 positive (of any COVID-19 episode, including reinfections) during the 21 days before the date of ICU admission OR on day 1 or day 2 of admission. |
| **Length of ICU Stay** | Patient's length of stay in ICU, with admission counted as day 1. |
| **Transfer between ICUs*** | **No/Yes**. Transfer directly from one ICU to another ICU at any time during the continuous ICU stay (CIS). |

| | |
|---|---|
| **ICU-acquired bloodstream infection (BSI)** | A case of ICU-acquired BSI was defined as a positive blood culture for bacteria or *Candida* species isolated from the patient's blood from day three onwards of their ICU admission until two days after ICU discharge, and who has not previously had the same organism isolated from blood within the same 14-day period.<br><br>An ICU-acquired positive blood specimen arising at least 14 days from any previous ICU-acquired positive blood specimen was considered a new episode of infection. |
| **Mortality Status** | **Alive/Died.** Mortality status on discharge from ICU. |
| **Patient Origin** | **Community/Hospital**. Derived from source of admission. |
| **Sex** | **Male/Female** |
| **Survival Time** | Number of days from day three of admission (inclusive) to the first of the following events: onset of infection, death, or discharge plus two days. |
| **Time-period** | **Comparator:** Admissions between the 01-03-2018 and 30-11-2019 and discharged prior to the 28-12-2019.<br>**Pandemic Wave 1:** Admissions between the 01-03-2020 and 31-07-2020 and discharged prior to 28-12-2021.<br>**Pandemic Wave 2a**: Admissions between the 01-08-2020 and 27-12-2020 and discharged prior to 28-12-2021.<br>**Pandemic Wave 2b:** Admissions between the 28-12-2020 and 17-05-2021 and discharged prior to 28-12-2021.<br>**Pandemic Wave 3**: Admissions between the 18-05-2021 and 30-11-2021 and discharged prior to 28-12-2021. |
| **Trauma Admission** | **No/Yes**. Admission to ICU prompted by blunt or penetrating trauma. |

*When included in regression models, variable censored at date of first ICU infection, or death, or discharge plus 2 days, whichever occurs first.