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Mortality amongst hospitalized COVID-19 cases by acquisition and pandemic wave in Wales, UK, February 2020—March 2022

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SUMMARY

Background: Hospital populations are vulnerable to COVID-19, but the relative severity of hospital acquisition compared to community is unknown. We investigated differences in mortality between hospital and community acquired cases in Wales.

Methods: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction tests from February 2020 to March 2022 were linked with hospital admissions to identify likely hospital-acquired cases. All-cause mortality within 28 days of a positive SARS-CoV-2 were measured by source of acquisition. Multi-variable logistic regression was used to compare mortality by source of acquisition, adjusting for confounders, computing adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Results: There were 25,263 hospital-acquired cases of COVID-19 and 5490 (22%) deaths in the study period. Although significant on univariate analysis, adjustment for confounding showed no association with increased mortality for hospital-acquired cases compared with cases admitted with COVID-19 (aOR 0.8, 95% CI 0.7-0.8). Vaccination (aOR 0.6, 95% CI 0.5-0.7) and infection in later pandemic waves (aOR 0.5, 95% CI 0.4-0.6) were associated with lower mortality; older age (≥85 vs <25 years: aOR 76.4, 95% CI 41.8-160.5) and male sex (aOR 1.5, 95% CI 1.4-1.6) were associated with higher mortality.

Conclusion: One in five hospitalised COVID-19 cases died within a month of infection. Mortality in nosocomial cases was not worse than those admitted with COVID-19, possibly reflecting early identification of nosocomial cases through screening.

Introduction

Healthcare-associated infections (HCAIs) pose a serious threat to patient safety, and increase the operational expenditure of the UK National Health Service (NHS). Monitoring and measuring HCAIs provide important proxy indicators for adherence to infection prevention practices in hospitals. Nosocomial transmission of coronavirus disease 2019 (COVID-19) emerged as a significant concern worldwide, accounting for up to 40% of all confirmed cases [1]. Hospital-acquired cases of COVID-19 contributed significantly to the burden of COVID-19 in hospitals in Wales [2]. More than 25,000 nosocomial cases have been recorded in national surveillance in Wales, with increases experienced in every pandemic wave [3].

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Deaths in patients with COVID-19 are an important measure of patient outcome and intervention success. Interpretation of crude death rates is complex in the context of the likely source of acquisition of COVID-19. One might expect higher death rates in patients with nosocomial COVID; these patients have already been in hospital for >1 week prior to their positive COVID-19 test, and are therefore likely to be in poorer general health and are probably older than those with community-acquired COVID-19 admitted to hospital. Community-acquired cases admitted to hospital may differ in their acuteness of infection, and their access to specialist health care may have been delayed. A study across 18 major hospitals in Wales during the first wave of the COVID-19 pandemic reported that 30-day mortality was higher in patients with nosocomial COVID-19 (38–42%) than in those with community-acquired COVID-19 (31–35%) [2].

Timing of disease within the pandemic period and vaccination status will also influence outcome. Over the pandemic period, there have been improvements in patient management and treatments for COVID-19, and the development of effective vaccines and their high uptake, so one might expect deaths to fall over time. Different variants of COVID-19 have been predominant at different times in the pandemic, and some may be associated with higher disease severity and mortality.

Multiple investigations are being undertaken regarding the management and impact of the COVID-19 pandemic, but learning from these processes will only become available over time because of the volume of information to cover [4,5]. This study aimed to describe all-cause mortality in hospitalized COVID-19 patients, and investigate differences between cases who likely acquired their infection in hospital and those who acquired it in the community, but were admitted to hospital, to provide a broad overview of the most severe outcome of COVID-19.

Methods

Data sources

Results of all severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction tests conducted in Wales are held in the all Wales laboratory information management system, used by Public Health Wales Communicable Disease Surveillance Centre for COVID-19 surveillance. Testing episodes for the study timeframe were deduplicated based on 42 days.

Hospital admission dates and dates of death from patient administration systems are available via ICNet, an infection prevention case management and reporting system used across all secondary care settings in Wales. COVID-19 vaccination status is available from the Welsh Immunization Service database.

COVID-19 case data with specimen dates from 27th February 2020 to 31st March 2022 were extracted, and cases were linked to their hospital admissions, dates of death and vaccination status using NHS number. Only COVID-19 cases with a specimen taken in a hospital setting were included. The earliest admission date to the health board (where admission was continuous but in multiple different hospitals) was used for comparison with the specimen collection date to categorize likely acquisition.

Case definitions

Acquisition

Definitions of nosocomial COVID-19 were agreed across the UK based on days between admission to secondary care and the positive SARS-CoV-2 test specimen collection date. For patients in hospital.

- Non-hospital onset (non-HO): specimens taken on day of admission or day after admission (days 1 and 2).
- Hospital onset, indeterminate healthcare associated (HO-indeterminate): specimens taken on days 3–7 of admission.
- Hospital onset, probable healthcare associated (HO-probable): specimens taken on days 8–14 of admission.
- Hospital onset, healthcare associated (HO): specimens taken >14 days after admission.

Pandemic wave

The pandemic wave was categorized based on the predominant variant causing infection. Wales experienced four waves over the study timeframe: Wave 1, 27th February 2020 to 26th July 2020; Wave 2, 27th July 2020 to 16th May 2021; Wave 3, 17th May 2021 to 19th December 2021; and Wave 4, 20th December 2021 to 31st March 2022 (end of study timeframe).

Vaccination status

Vaccination status at date the specimen was taken was used.

- Unvaccinated: no history of COVID-19 vaccination within the 14 days prior to specimen date or first vaccination within 14 days prior to specimen date.
- One dose: specimen date >14 days after COVID-19 vaccination date with either no documentation of a second dose or second dose within 14 days prior to specimen date.
- Two or more doses: specimen date >14 days after date of second COVID-19 vaccination date.

Outcome

The primary outcome was all-cause mortality (mortality). This was defined as death due to any cause within 28 days of a positive SARS-CoV-2 test.

Data analysis

Continuous variables are presented as median with interquartile range (IQR), and categorical variables are presented as proportion. The proportion of COVID-19 deaths was compared between acquisition categories, and odds ratio (OR) with 95% confidence interval (95% CI) were calculated. Univariate analysis was performed, and a multi-variate logistic regression model was developed to adjust for potential confounding in the comparison between acquisition categories. Age group, sex, pandemic wave and vaccination status were included in the model. Each acquisition category was compared with the reference anonymized data group of the non-HO cases. R Version 4.1.3 was used for statistical analysis. $P<0.05$ was considered to indicate significance.

Table I
Mortality in patients with coronavirus disease 2019 by likely source of acquisition and pandemic wave, Wales, UK, 27th February 2020–31st March 2022

Acquisition	Wave 1[a]		Wave 2[b]		Wave 3[c]		Wave 4[d]		Total	
	Deaths *N* (%)	Cases *N*	Deaths *N* (%)	Cases *N*	Deaths *N* (%)	Cases *N*	Deaths *N* (%)	Cases *N*	Deaths *N* (%)	Cases *N*
Non-HO	508 (30.3)	1676	878 (24.4)	3595	381 (15.2)	2514	209 (9.9)	2107	1976 (20.0)	9892
HO-indeterminate	168 (31.8)	529	404 (29.5)	1371	85 (18.0)	473	126 (12.8)	985	783 (23.3)	3358
HO-probable	251 (38.9)	645	541 (29.9)	1812	70 (20.5)	342	125 (13.7)	912	987 (26.6)	3711
HO	373 (30.7)	1214	887 (25.9)	3427	175 (15.5)	1129	309 (12.2)	2532	1744 (21.0)	8302
Total	1300 (32.0)	4064	2710 (26.6)	10205	711 (15.9)	4458	769 (11.8)	6536	5490 (21.7)	25,263

HO, hospital onset.
[a] 27th February 2020–26th July 2020.
[b] 27th July 2020–16th May 2021.
[c] 17th May 2021–19th December 2021.
[d] 20th December 2021–31st March 2022.

Ethical approval

This study used anonymized national data that were collected for other reasons; as such, ethical approval was not required for this work.

Results

Characteristics of hospitalized COVID-19 cases

In total, there were 25,263 hospitalized COVID-19 cases during the study period (Table I). The median age of cases was 76 (IQR 62–85) years, with approximately half aged >74 years and 12% aged <45 years. Fifty one percent were female. Forty-eight percent of cases had a positive SARS-CoV-2 test >7 days after hospital admission (Table I).

Characteristics of deceased hospitalized COVID-19 cases

There were 5490 (22%) deaths within 28 days of a positive SARS-CoV-2 test in the hospitalized COVID-19 cases. Mortality was 20%, 23%, 27% and 21% for non-HO, HO-indeterminate, HO-probable and HO COVID-19 cases, respectively. The median age of deceased cases was 81 (IQR 73–88) years, with 57% aged >74 years and <3% aged <45 years (Table II). Mortality increased as age increased in all acquisition categories. Mortality increased in HO cases compared with community-acquired cases in younger age groups, whereas it decreased in older age groups (Table III).

Table II
Univariable and multi-variable analysis of risk factors for mortality in hospitalized cases of coronavirus disease 2019, Wales, UK, 27th February 2020–31st March 2022

Factor		Deaths *N* (%)	Alive *N* (%)	Crude odds ratio (95% CI, *P*-value)	Adjusted odds ratio (95% CI, *P*-value)
Age (years)	0–24	9 (0.7)	1259 (99.3)	Ref	Ref
	25–44	40 (2.1)	1828 (97.9)	3.1 (1.6–6.8, 0.003)	3.3 (1.7–7.3, 0.001)
	45–64	484 (12.5)	3383 (87.5)	20.0 (10.9–41.9, <0.001)	19.6 (10.7–41.3, <0.001)
	65–74	994 (22.6)	3411 (77.4)	40.8 (22.4–85.2, <0.001)	42.6 (23.3–89.6, <0.001)
	75–84	1891 (26.6)	5230 (73.4)	50.6 (27.9–105.6, <0.001)	56.1 (30.7–117.7, <0.001)
	≥85	2072 (30.8)	4662 (69.2)	62.2 (34.3–129.8, <0.001)	76.4 (41.8–160.5, <0.001)
Sex	Female	2415 (18.8)	10465 (81.2)	Ref	Ref
	Male	3075 (24.8)	9308 (75.2)	1.4 (1.3–1.5, <0.001)	1.5 (1.4–1.6, <0.001)
Wave	Wave 1[a]	1300 (32.0)	2764 (68.0)	Ref	Ref
	Wave 2[b]	2710 (26.6)	7495 (73.4)	0.8 (0.7–0.8, <0.001)	0.8 (0.7–0.9, <0.001)
	Wave 3[c]	711 (15.9)	3747 (84.1)	0.4 (0.4–0.4, <0.001)	0.8 (0.7–0.9, 0.004)
	Wave 4[d]	769 (11.8)	5767 (88.2)	0.3 (0.25–0.31, <0.001)	0.5 (0.4–0.6, <0.001)
Acquisition	Non-HO	1976 (20.0)	7916 (80.0)	Ref	Ref
	HO-indeterminate	783 (23.3)	2575 (76.7)	1.2 (1.1–1.3, <0.001)	1.0 (0.9–1.1, 0.6)
	HO-probable	987 (26.6)	2724 (73.4)	1.5 (1.3–1.6, <0.001)	1.0 (0.9–1.1, 0.4)
	HO	1744 (21.0)	6558 (79.0)	1.1 (1.0–1.1, 0.09)	0.8 (0.7–0.8, <0.001)
Vaccination status	Unvaccinated	4042 (26.0)	11497 (74.0)	Ref	Ref
	One dose	176 (15.5)	959 (84.5)	0.5 (0.4–0.6, <0.001)	0.5 (0.5–0.6, <0.001)
	Two or more doses	1272 (14.8)	7317 (85.2)	0.49 (0.46–0.53, <0.001)	0.6 (0.5–0.7, <0.001)

HO, hospital onset; CI, confidence interval.
[a] 27th February 2020–26th July 2020.
[b] 27th July 2020–16th May 2021.
[c] 17th May 2021–19th December 2021.
[d] 20th December 2021–31st March 2022.

Table III
Mortality in hospitalized patients with coronavirus disease 2019 by likely source of acquisition and age group, Wales, UK, 27th February 2020–31st March 2022

Acquisition/age		0–24 years	25–44 years	45–64 years	65–74 years	75–84 years	≥85 years
Non-HO	Deaths *N* (%)	4 (0.4)	21 (1.6)	241 (12.3)	431 (24.6)	676 (29.7)	603 (37.3)
	Alive *N* (%)	1012 (99.6)	1257 (98.4)	1717 (87.7)	1318 (75.4)	1600 (70.3)	1012 (62.7)
	OR (95% CI, *P*-value)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
HO-indeterminate	Deaths *N* (%)	2 (3.3)	7 (3.3)	65 (11.4)	140 (21.9)	276 (28.1)	293 (32.7)
	Alive *N* (%)	58 (96.7)	202 (96.7)	506 (88.6)	498 (78.1)	707 (71.9)	604 (67.3)
	OR (95% CI, *P*-value)	8.7 (1.2–45.7, 0.013)	2.1 (0.8–4.7, 0.1)	0.9 (0.7–1.2, 0.6)	0.9 (0.7–1.1, 0.2)	0.9 (0.8–1.1, 0.3)	0.8 (0.7–0.9, 0.019)
HO-probable	Deaths *N* (%)	1 (4.2)	6 (6.4)	71 (16.0)	146 (22.9)	349 (28.2)	414 (32.5)
	Alive *N* (%)	23 (95.8)	88 (93.6)	374 (84.0)	492 (77.1)	887 (71.8)	860 (67.5)
	OR (95% CI, *P*-value)	11.0 (0.6–78.0, 0.035)	4.1 (1.5–9.8, 0.003)	1.4 (1.0–1.8, 0.039)	0.9 (0.7–1.1, 0.4)	0.9 (0.8–1.1, 0.4)	0.8 (0.7–0.9, 0.007)
HO	Deaths *N* (%)	2 (1.2)	6 (2.1)	107 (12.0)	277 (20.1)	590 (22.5)	762 (25.8)
	Alive *N* (%)	166 (98.8)	281 (97.9)	786 (88.0)	1103 (79.9)	2036 (77.5)	2186 (74.2)
	OR (95% CI, *P*-value)	3.1 (0.4–15.7, 0.2)	1.3 (0.5–3.0, 0.6)	1.0 (0.8–1.2, 0.8)	0.8 (0.7–0.9, 0.002)	0.7 (0.6–0.8, <0.001)	0.6 (0.5–0.7, <0.001)

HO, hospital onset; CI, confidence interval.

Mortality was higher in males (25%) than females (19%). Mortality decreased within each pandemic wave.

Univariate and multi-variate logistic regression

In univariate analysis, each hospital onset category was significantly associated with higher mortality compared with non-HO cases (Table II). Older age groups, male sex, infection in the first wave of the pandemic and being unvaccinated were also significantly associated with higher mortality in hospitalized COVID-19 cases (Table II).

Within the multi-variate model, there was no evidence that cases who acquired COVID-19 in hospital were at increased risk of death compared with non-HO cases, after statistical adjustment for confounding by the other variables within the model. Age group, sex, pandemic wave and vaccination status remained significantly associated with mortality. The odds of mortality in cases aged >85 years was 76 times higher compared with those aged <25 years, and was 50% higher in males compared with females (Table II). The odds of mortality decreased by 50% in Wave 4 compared with Wave 1. There was a 40–50% decrease in the odds of death in vaccinated patients compared with unvaccinated patients.

Discussion

The wide clinical disease spectrum, including asymptomatic infection, and the limited knowledge of health systems worldwide regarding prevention and control of COVID-19 contributed to its high nosocomial burden. Despite frequent changes in testing policies for patients and healthcare workers, hospital admission criteria and infection prevention practices, healthcare settings in Wales experienced large COVID-19 outbreaks. High community prevalence, asymptomatic infections in healthcare workers, lack of single rooms, lack of space to maintain patient pathways, poor adherence to personal protective equipment, and patient transfers likely facilitated transmission within and between healthcare settings [6].

Outcomes of patients with hospital-acquired infection compared with patients admitted to hospital with community-acquired infection are difficult to predict. Patients in hospital are likely to be older and in poorer general health than their community counterparts, and therefore might be expected to have poorer outcomes. Within a hospital setting, however, they are more likely to be identified at an early stage of infection because of frequent screening, and have access to immediate treatment, and therefore might be expected to have better outcomes.

Reports from the scientific literature are mixed regarding whether nosocomial acquisition of COVID-19 is a risk factor for mortality. Studies have found a general increased risk associated with nosocomial acquisition [7], or in defined groups such as younger age groups [8] or cancer patients [8,9]. Potential mechanisms underlying these findings include pre-existing diseases and frailty among elderly patients admitted for longer durations during the COVID-19 pandemic [10,11]. Other investigations have found no significant differences in mortality between hospital- and community-acquired cases [10,12] after controlling for confounders.

This study investigated 28-day all-cause mortality in hospitalized patients with COVID-19 in Wales, and found that, overall, 22% of COVID-19 cases identified in hospital in Wales died

within 28 days. Overall mortality was higher in those cases who likely acquired their infection in hospital, with some variation by age. After controlling for confounding variables (age, sex, pandemic wave and vaccination status), the odds of mortality were not significantly higher in these cases. Most studies available in the literature are based on earlier waves of the pandemic, whereas this analysis is based on cases from the start of the pandemic to March 2022. A study in Scotland to the end of March 2022 also found no association between nosocomial acquisition and mortality, after controlling for potential confounding factors, including comorbidities [13]. Similarly, a study from Germany to mid-May 2022 reported decreased mortality in nosocomial COVID-19 cases compared with community-acquired cases after adjusting for confounding factors [14].

Factors that would be expected to be associated with mortality were found to be associated in this analysis, with significantly higher odds of death in older age groups and male patients. Vaccinated patients had reduced odds of mortality compared with unvaccinated patients. Each pandemic wave had reduced odds of mortality compared with Wave 1, likely reflecting improved treatment, patient management and availability of effective vaccination developed through the pandemic period.

This study has some limitations. Only routinely collected surveillance data sets were used, which limited the potential confounding variables available for inclusion. Comorbidities, pre-existing diseases, immune status and clinical symptoms were not available in the routine surveillance data to include in the analysis. However, it is likely that there would have been a high degree of collinearity between comorbidities, pre-existing diseases, immune status and older age. Secondly, all-cause mortality was measured as the primary outcome, rather than COVID-19-specific mortality. This may explain why it was not possible to see an increased benefit from multiple vaccine doses. Finally, the exclusion of asymptomatic screening cases would have given a more meaningful measure of outcomes associated with COVID-19. The hospital testing policy in Wales for most of the study period included admission and routine patient asymptomatic screening. The reduced odds of mortality in nosocomial cases in older age groups and on multi-variable analysis may reflect an increased likelihood of long-stay patients being identified through regular asymptomatic screening.

The UK COVID-19 Public Inquiry is reviewing management of the pandemic in hospitals, including infection prevention and control [4]. Health boards and trusts within NHS Wales, with the support of the NHS Wales Delivery Unit, are investigating patient safety incidents of suspected nosocomial COVID-19 [5]. These investigations will further inform understanding of causes and outcomes of nosocomial COVID-19 in the UK, and actions that can be taken for future pandemic preparedness.

Author contributions

PR, JB, VM and MM conceptualized the study. PR and JB collected, analysed and interpreted the data. VM established the data collection systems, and checked the quality of data and analysis. PR drafted the first manuscript. JB, VM and MM commented on and edited the manuscript. All authors commented on or edited drafts and approved the final version of the manuscript.

Conflict of interest statement

None declared.

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