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Comparative analysis of characteristics and outcomes in hospitalized COVID-19 patients infected with different SARS-CoV-2 variants between January 2020 and April 2022 – A retrospective single-center cohort study

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ABSTRACT

Background: Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the roll-out of vaccines and therapeutic agents, as well as the emergence of novel SARS-CoV-2 variants, have shown significant effects on disease severity.
Methods: Patients hospitalized at our center between January 2020 and April 2022 were attributed to subgroups depending on which SARS-CoV-2 variant was predominantly circulating in Germany: (i) Wild-type: January 1, 2020, to March 7, 2021, (ii) Alpha variant: August 3, 2021, to June 27, 2021, (iii) Delta variant: June 28, 2021, to December 26, 2021, and (iv) Omicron variant: December 27, 2021, to April 30, 2022.
Results: Between January 2020 and April 2022, 1500 patients with SARS-CoV-2 infections were admitted to the University Medical Center Hamburg-Eppendorf. The rate of patients who were admitted to the intensive care unit (ICU) decreased from 31.2% (n = 223) in the wild-type group, 28.5% (n = 72) in the Alpha variant group, 18.8% (n = 67) in the Delta variant group, and 13.4% (n = 135) in the Omicron variant group. Also, in-hospital mortality decreased from 20.6% (n = 111) in the wild-type group, 17.5% (n = 30) in the Alpha variant group, 16.8% (n = 33) in the Delta variant group, and 6.6% (n = 39) in the Omicron variant group. The median duration of hospitalization was similar in all subgroups and ranged between 11 and 15 days throughout the pandemic.
Conclusions: In-hospital mortality and rate of ICU admission among hospitalized COVID-19 patients steadily decreased throughout the pandemic. However, the practically unchanged duration of hospitalization demonstrates the persistent burden of COVID-19 on the healthcare system.

Background

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the roll-out of vaccination campaigns and the implementation of different therapeutic agents and treatment strategies have significantly affected patient morbidity and mortality. Also,

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multiple severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants have emerged, which differ in transmissibility, pathogenicity, and capacity for immune evasion. The Alpha variant (B.1.1.7) was first reported in the United Kingdom in November 2020. In Germany, it superseded the previously circulating SARS-CoV-2 wild-type by February 2021 [1]. The Delta variant (B.1.617.2) was first reported in India in October 2020 and became the predominant SARS-CoV-2 variant in Germany in June 2021 [2]. In November 2021, the Omicron variant (B.1.1.529) emerged and was rapidly designated a new variant of concern by the World Health Organization (WHO). It replaced the Delta variant as the predominant SARS-CoV-2 variant in Germany in January 2022 [3–5]. Several studies have assessed the clinical outcomes among COVID-19 patients, but real-world data directly comparing hospitalized COVID-19 patients with different SARS-CoV-2 variants within the same clinical setting are scarce. We have previously reported on the clinical characteristics and disease outcomes of COVID-19 during the first months of the pandemic in 2020 [6,7]. In this present study, we compared the clinical characteristics in a real-world cohort of COVID-19 patients hospitalized at the University Medical Center Hamburg-Eppendorf during different phases of the pandemic between January 2020 and April 2022. We chose this real-world, high-resolution analysis to better understand the changes in epidemiology, the influence of COVID-19 vaccinations and specific antiviral therapies on disease outcomes of hospitalized COVID-19 patients, and the interactions between patients and the healthcare system. Thus, we hope to potentially project future resources needed for hospitalized COVID-19 patients and identifies areas for improvement of care.

Materials and methods

Study design

All patients who presented at the University Medical Center Hamburg-Eppendorf with RT-PCR-confirmed SARS-CoV-2 infections between January 2020 and April 2022 were analyzed by a detailed review of the electronic patient files, which are available for all patients on regular wards as well as on the intensive care unit (ICU). Patients younger than 18 and those who presented at our emergency department or as outpatients in our clinics but did not require hospitalization were not included in the current study. We attributed patients to one of the following four time periods depending on which SARS-CoV-2 variant was predominantly circulating in Germany: (i) Wild-type: January 1, 2020, to March 7, 2021, (ii) Alpha variant: August 3, 2021, to June 27, 2021, (iii) Delta variant: June 28, 2021, to December 26, 2021, and (iv) Omicron variant: December 27, 2021, to April 30, 2022 [5,8]. The study was reviewed and approved by the Ethics Committee of the Medical Council of Hamburg (WF-052/20).

Clinical data

Patients who were admitted before the first COVID-19 vaccine BNT162b2 (Pfizer–BioNTech, Comirnaty) received conditional marketing authorization in the European Union on December 21, 2020 [9], were classified as unvaccinated. The age-adjusted Charlson Comorbidity Index (aaCCI) was used to categorize preexisting medical conditions. Patients who required respiratory support (invasive mechanical ventilation after endotracheal intubation, non-invasive ventilation (NIV), high-flow oxygen therapy, low-flow oxygen therapy) were assigned to the most invasive form of respiratory support that was required. Nosocomial SARS-CoV-2 infection was defined as a positive RT-PCT four days after being admitted to the hospital. The median duration of hospitalization was calculated only for patients that were admitted with SARS-CoV-2 infections and did not contract nosocomial infections.

Statistical analyses

Continuous variables are expressed as the median and interquartile range (IQR) and compared with the Kruskal-Wallis test where reasonable. Categorical variables are expressed as numbers (%) and compared by Fisher's exact test where reasonable. Since we did not have access to follow-up data for all patients, we were not able to access 120-day mortality. Instead, we chose to compare the proportion of patients in the respective subgroups that were discharged alive during the first 120 days of hospitalization was compared via log-rank test. We further compared in-hospital mortality in unvaccinated patients and in those who had received at least two COVID-19 vaccine doses for hospitalized patients with different SARS-CoV-2 variants. To minimize confounding from sex, age, aaCCI, and immunocompromised state, a propensity score was generated for each patient. Patients in the respective subgroup group were matched to the patient at a 1:1 ratio using a nearest neighbor matching algorithm. P values less than 0.05 are considered statistically significant. Statistical analyses were performed within the R environment (version 1.2.5.002) on a Mac OS X and with SPSS, version 26 (IBM Corp., Armonk, New York, USA). Figures were designed using GraphPad Prism, version 9 for macOS (GraphPad Software, La Jolla, California, USA).

Results

Characterization of the study population

Detailed baseline characteristics of the study population are presented in Table 1. Between January 2020 and April 2022, a total of 1500 hospitalized patients with SARS-CoV-2 infections were treated at the University Medical Center Hamburg-Eppendorf (Fig. 1). Of those, 36.0% (n = 540) were assigned to the wild-type group, 11.4% (n = 171) to the Alpha variant group, 13.1% (n = 196) to the Delta variant group, and 39.5% (n = 593) to the Omicron variant group depending on which SARS-CoV-2 variant was predominantly circulating in Germany. Data on isolated SARS-CoV-2 variants in patients in our study cohort are provided in **Supplemental** Table 1 and **Supplemental** Fig. 1. No patient was infected with multiple SARS-CoV-2 variants during any single disease episode. Two patients were admitted twice with SARS-CoV-2 infections throughout the pandemic, once in the wild-type group and once in the Omicron variant group. The median age was higher in patients in the wild-type group (61 years; IQR: 44–73 days) and the Omicron variant group (60 years; IQR: 41–74 days) compared to the Alpha variant group (56 years; IQR: 42–65 days) and the Delta variant group (55 years; IQR: 39–70 days). Overall, 42.9% (n = 644) of the study population were female without relevant differences in sex distribution between the subgroups. The number of patients in an immunocompromised state due to underlying medical conditions or immunosuppressive therapy continuously increased throughout the pandemic: 22.2% (n = 120) of patients in the wild-type group, 22.8% (n = 39) in the Alpha variant group, 28.6% (n = 56) in the Delta variant group and 34.4% (n = 204) in the Omicron variant group were in an immunocompromised state. Also, the distribution of particular high-risk subgroups such as patients with hematological malignancies, hematopoietic stem-cell transplantation recipients and solid organ transplant recipients was similar throughout the pandemic. Median aaCCI was between 2 and 3 in all subgroups. While vaccination status was not available for all patients in our study cohort, the rate of patients who had received at least two COVID-19 vaccine doses steadily increased throughout the study period from 0.2% (n = 1) in the wild-type group, 1.8% (n = 3) in the Alpha variant group, 37.8% (n = 74) in the Delta variant group, and 43.7% (n = 259) in the Omicron group. The rate of nosocomial SARS-CoV-2 infections among the study cohort increased from 12.4% (n = 67) in the

Table 1
Baseline characteristics of COVID-19 patients hospitalized during different phases of the pandemic.

	Total	**Wild-type** predominant (January 1, 2020 – March 7, 2021)	**Alpha** predominant (March 8, 2021 – June 27, 2021)	**Delta** predominant (June 28, 2021 -December 26, 2021)	**Omicron** predominant (December 27, 2021 – April 30, 2022)
n (%)	1500	540	171	196	593
Sex, n (%)					
Female	644 (42.9)	227 (42.0)	74 (43.3)	86 (43.9)	257 (43.3)
Male	856 (57.1)	313 (58.0)	97 (56.7)	110 (56.1)	336 (56.7)
Age (years)					
Median	60	61	56	55	60
IQR (25–75)	44–73	49–74	42–65	39–70	41–74
Immunocompromised state, n (%)					
Total	419 (27.9)	120 (22.2)	39 (22.8)	56 (28.6)	204 (34.4)
Haematological malignancy	112 (7.5)	36 (6.7)	10 (5.8)	15 (7.7)	51 (8.6)
HSCT	19 (1.3)	7 (1.3)	2 (1.2)	1 (0.5)	9 (1.5)
Solid Organ transplant	93 (6.2)	28 (5.2)	4 (2.3)	10 (5.1)	51 (8.6)
Chemotherapy	111 (7.4)	40 (7.4)	8 (4.4)	16 (8.2)	47 (7.9)
B-cell depletion	50 (3.3)	18 (3.3)	2 (1.2)	7 (3.6)	23 (3.9)
Methotrexate	18 (1.2)	5 (0.9)	0 (0.0)	4 (2.0)	9 (1.5)
mTOR Inhibitors	36 (2.4)	16 (3.0)	2 (1.2)	3 (1.5)	15 (2.5)
Anti-TNF-α	9 (0.6)	5 (0.9)	1 (0.6)	0 (0.0)	3 (0.5)
Anakinra	5 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.5)
aaCCI, n (%)					
Median	3	3	2	2	3
IQR, 25–75	1 – 5	1 – 5	0–4	0–4	1–5
0	361 (24.1)	95 (17.6)	55 (32.2)	65 (33.2)	146 (24.6)
1–2	376 (25.1)	155 (28.7)	55 (32.2)	53 (27.0)	113 (19.1)
3–4	349 (23.3)	144 (26.7)	38 (22.2)	37 (18.9)	130 (21.9)
≥ 5	414 (27.6)	146 (27.0)	23 (13.5)	41 (20.9)	204 (34.4)
Vaccination status, n (%)					
≥ 2 vaccine doses	337 (22.5)	1 (0.2)	3 (1.8)	74 (37.8)	259 (43.7)
1 vaccine dose	43 (2.9)	1 (0.2)	15 (8.8)	11 (5.6)	16 (2.7)
Unvaccinated	618 (41.2)	504 (93.3)	4 (2.3)	56 (28.6)	54 (9.1)
No data	502 (33.5)	34 (6.3)	149 (87.1)	55 (28.1)	264 (44.5)

IQR, interquartile range; HSCT, hematologic stem cell transplant; aaCCI, age-adjusted Charlson Comorbidity Index

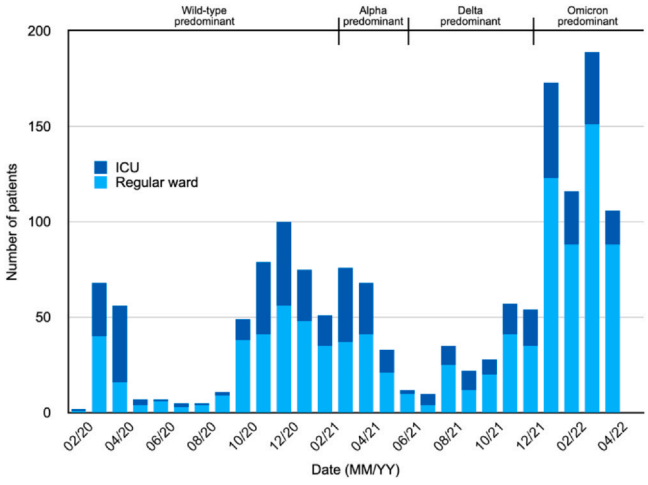

Fig. 1. Number of COVID-19 patients hospitalized at the University Medical Center Hamburg-Eppendorf between January 2020 and April 2022**.** Patients are attributed to the respective month depending on the date of hospital admission. ICU, intensive care unit.

wild-type group, 4.7% (n = 8) in the Alpha variant group, 11.7% (n = 23) in the Delta variant group, and 28.2% (n = 167) in the Omicron variant group. In the wild-type group (52.2%, n = 35 vs 18.0%, n = 85) and the Delta variant group (47.8%, n = 11 vs 26.0%, n = 45) the rate of patients in an immunocompromised state was higher among patients with community-acquired SARS-CoV-2 infections than in those with nosocomial infections. In contrast, in the Alpha variant group (12.5%, n = 1 vs 23.3%, n = 38) and the Omicron variant group (32.9%, n = 55 vs 35.0%, n = 149), the rate of patients in an immunocompromised state was lower in those with community-acquired infections compared to those with nosocomial infections.

Clinical course

Data on the clinical course of the four SARS-CoV-2 variant subgroups are shown in Table 2. Throughout the COVID-19 pandemic, in-hospital mortality markedly decreased from 20.6% (n = 111) in the wild-type group, 17.5% (n = 30) in the Alpha variant group, 16.8% (n = 33) in the Delta variant group, and 6.6% (n = 39) in the Omicron variant group. In-hospital mortality among patients above 65 of age was significantly higher than among those younger than 65 years of age in all subgroups but the Alpha variant group (Fig. 2). The rate of patients who were admitted to the ICU also decreased from 31.2% (n = 223) in the wild-type group, 28.5% (n = 72) in the Alpha variant group, 18.8% (n = 67) in the Delta variant group, and 13.4% (n = 135) in the Omicron variant group. In total, 20.1% (n = 301) of patients required invasive ventilation with the need for endotracheal intubation, 2.3% (n = 35) required high-flow oxygen therapy (HFOT), 3.5% (n = 53) non-invasive ventilation (NIV) and 22.6% (n = 339) low-flow oxygen therapy (LFOT). The rate of patients requiring invasive ventilation steadily decreased throughout the pandemic from 30.7% (n = 116) in the wild-type group, 29.8% (n = 51) in the Alpha variant group, 23.0% (n = 45) in the Delta variant group, and 6.6% (n = 39) in the Omicron variant group. The rate of patients who were treated with non-invasive ventilation (NIV) initially increased from the wild-type group to the Alpha variant and Delta variant group, which may reflect the development of stepwise treatment strategies with the observance of all relevant anti-infectious precautions for COVID-19 patients with respiratory failure [10,11]. The number of patients receiving extracorporeal membrane oxygenation (ECMO) decreased from 14.4% (n = 78) in the wild-type group, 18.7% (n = 32) in the Alpha variant group, 11.2% (n = 22) in the Delta variant group, and

Table 2
Clinical outcomes of COVID-19 patients hospitalized during different phases of the pandemic.

	Total	**Wild-type** predominant (January 1, 2020 – March 7, 2021)	**Alpha** predominant (March 8, 2021 – June 27, 2021)	**Delta** predominant (June 28, 2021 -December 26, 2021)	**Omicron** predominant (December 27, 2021 – April 30, 2022)
Duration of hospitalisation (days)[1]					
Median	12	11	15	15	12
IQR(25–75)	5–24	5–23	8–49	6–20	4–33
Nosocomial infection	265 (17.7)	67 (12.4)	8 (4.7)	23 (11.7)	167 (28.2)
ICU admission, n (%)	497 (31.1)	223 (41.3)	72 (28.5)	67 (18.8)	135 (13.4)
ECMO, n (%)	110 (7.3)	56 (10.4)	29 (17.0)	24 (12.2)	1 (0.2)
Renal replacement therapy, n (%)	153 (10.2)	78 (14.4)	32 (18.7)	22 (11.2)	21 (3.5)
Vasopressor therapy, n (%)	343 (22.9)	179 (33.1)	57 (33.3)	49(25)	58 (9.8)
Respiratory support, n (%)					
LFOT	339 (22.6)	134 (24.8)	30 (17.5)	52 (26.5)	123 (20.7)
HFOT	35 (2.3)	15 (2.8)	4 (2.3)	4 (2.0)	12 (2.0)
NIV	53 (3.5)	16 (3.0)	10 (5.8)	10 (5.1)	17 (2.9)
Invasive Ventilation	301 (20.1)	166 (30.7)	51 (29.8)	45 (23.0)	39 (6.6)
Deaths, n (%)	213 (14.2)	111 (20.6)	30 (17.5)	33 (16.8)	39 (6.6)

IQR, interquartile range; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; LFOT, low-flow oxygen therapy; HFOT, high-flow oxygen therapy; NIV, non-invasive ventilation
[1] patients with nosocomial infections were excluded from the calculation of duration of hospitalization

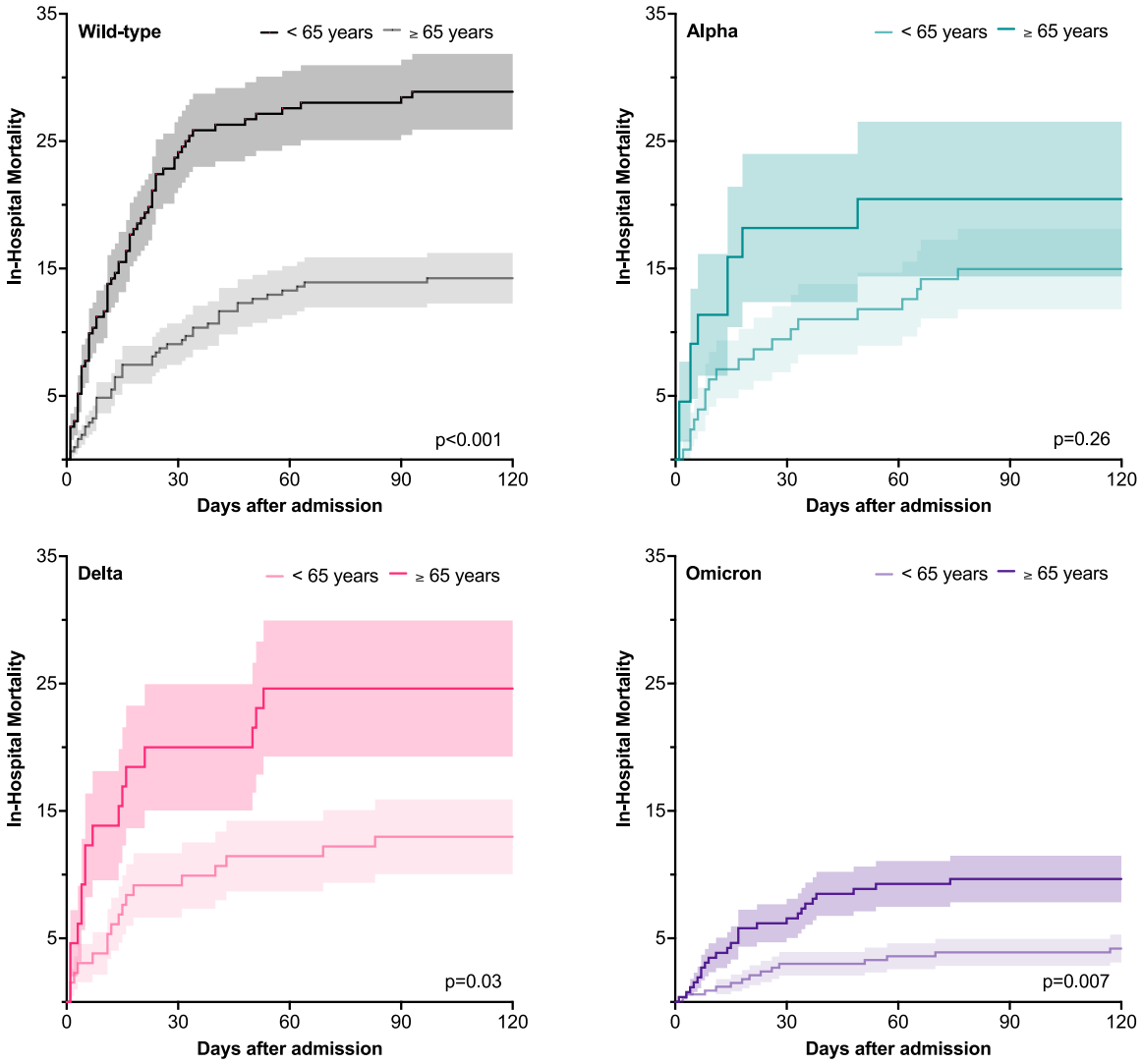

Fig. 2. In-hospital mortality in COVID-19 patients below and above 65 years of age hospitalized during different time periods. In-hospital mortality in COVID-19 patients below and above 65 years of age hospitalized during the wild-type predominant (A), Alpha variant predominant (B), Delta variant predominant (C), or Omicron variant predominant (D) time period at the University Medical Center Hamburg-Eppendorf compared by log-rank test.

0.2% (n = 1) in the Omicron variant group. Mortality among patients receiving ECMO was 67.9% (n = 38) in the wild-type group, 62.1% (n = 18) in the Alpha variant group, 58.3% (n = 14) in the Delta variant group, and 0% (n = 0) in the Omicron variant group. Also, the rate of patients who required new renal replacement therapy decreased over time. The median duration of hospitalization for the entire study period was 12 days (IQR: 5–24 days) and was similar in all subgroups. The different antiviral therapies, immunomodulatory therapies, and antibiotic agents patients received are shown in **Supplemental** Table 2. A total of 23.4% (n = 351) of COVID-19 patients received antiviral medication, 19.6% (n = 106) in the wild-type group, 14.6% (n = 25) in the Alpha variant group, 31.6% (n = 62) in the Delta variant group and 26.6% (n = 158) in the Omicron variant group. Given the date of licensing, availability or recommendation by national and international guidelines [12], nirmatrelvir/ritonavir (n = 16) and molnupiravir (n = 13) were only administered to patients in the Omicron variant group. Remdesivir and dexamethasone were used throughout the COVID-19 pandemic. In total, 19.6% (n = 106) of patients in the Omicron group, 14.6% (n = 25) in the Alpha group, 31.6% (n = 62) in the Delta group, and 26.6% (n = 158) in the Omicron group received at least one antiviral medication. Lopinavir/ritonavir (n = 9), hydroxychloroquine (n = 9), and convalescent plasma (n = 18) were only given to patients in the wild-type group during the early phases of the pandemic. While the monoclonal antibody casirivimab/imdevimab was mainly administered to patients in the Alpha variant group 0.84% (n = 6) and the Delta variant group 11.46% (n = 29), sotrovimab was primarily given to patients in the Omicron variant group 12.0% (n = 121) [13]. A total of 26.4% (n = 396) of COVID-19 patients received immunomodulatory therapy with dexamethasone, tocilizumab, or baricitinib: 28.1% (n = 152) in the wild-type group, 42.1% (n = 72) in the Alpha variant group, 40.8% (n = 80) in the Delta variant group, and 15.5% (n = 92) in the Omicron variant group. The rate of COVID-19 patients treated with antibiotics during the hospitalization steadily decreased from 59.6% (n = 322) in the wild-type group to 34.4% (n = 204) in the Omicron variant group.

Deceased patients in the Omicron variant group (December 27, 2021, to April 30, 2022)

To determine the risk factors for in-hospital mortality, particularly among patients with SARS-CoV-2 Omicron variant infections, we assessed clinical characteristics and disease outcomes of all 39 deceased patients in the Omicron group, as shown in Supplemental Table 3. The median age of those patients was 71 years (IQR 59–80), and 58% (n = 23) were male. COVID-19 vaccination status was available for 66.7% (n = 26) of patients. Of those, 15.4% (n = 4) were not vaccinated, and 84.6% (n = 22) had received two or three vaccine doses. Almost half of the patients (48.7%; n = 19) were in an immunocompromised state. The majority (66.7%; n = 26) were treated at the ICU, 41% (n = 16) received invasive mechanical ventilation after endotracheal intubation, and none received ECMO. Only 12.8% (n = 5) of deceased patients in the Omicron variant group received antiviral medication. While the role of COVID-19 in the death of those SARS-CoV-2-positive patients cannot be reliably determined in retrospect, 56.4% (n = 22) patients had additional severe acute diagnoses such as *Staphylococcus aureus* bacteremia, perforated cholecystitis, or heart failure, which were considered the primary diagnosis and main reason for death by treating physicians.

Propensity-score matched analysis of in-hospital mortality

We further compared in-hospital mortality between propensity-score-matched unvaccinated patients in the wild-type group and the delta variant and omicron variant group, respectively as well as between patients who had received at least two COVID-19 vaccine doses in the delta variant and omicron variant group. Those propensity-score matched groups did not differ in terms of sex, age, aaCCI, and rate of patients in an immunocompromised state (Supplemental Tables 4–6). In-hospital mortality did not differ between unvaccinated patients in the wild-type group and the Delta variant group (**Supplemental** Fig. 2), between unvaccinated patients in the wild-type group and the Omicron variant group (Supplemental Figure 3), and between vaccinated patients in the Delta variant group and the Omicron variant group (Supplemental Figure 4). Matched comparisons of in-hospital mortality between other vaccinated or unvaccinated subgroups were not performed due to small patient numbers.

Discussion

In this ongoing single-center cohort study [6,7], we assessed the clinical characteristics and outcome data of 1500 consecutive COVID-19 patients who were hospitalized at the University Medical Center Hamburg-Eppendorf between January 2020 and April 2022. Rather than stratifying the patients according to the year of admission, we decided to analyze the patients according to the respective SARS-CoV-2 virus variant primarily circulating at the time of infection.

The most important finding of the current study is that as the COVID-19 pandemic evolved, the overall in-hospital mortality of hospitalized COVID-19 patients at our university hospital steadily decreased from 20.6% in the wild-type group to 17.5% in the Alpha variant group, 16.8% in the Delta variant group, and 6.6% in the Omicron variant group. This trend towards a potentially less severe clinical course is also reflected by a decreasing rate of patients requiring ICU admission, respiratory support, renal replacement therapy, and vasopressor therapy, respectively. This improved outcome was observed in our study cohort even though patients in the Omicron variant group had a higher median age than patients in the Delta variant group. Also, aaCCI did not differ between the different subgroups and the rate of patients in an immunocompromised state being treated at our center with SARS-CoV-2 infections increased throughout the study period.

While we have compared patient outcomes of four different time periods depending on whichever SARS-CoV-2 variant was predominantly circulating in Germany, the reasons for the overall improved outcomes of hospitalized COVID-19 patients throughout the pandemic seem to be multifactorial. Real-life studies like ours are not able to reliably identify which of those abovementioned factors have the highest impact on patient outcomes.

First and foremost, COVID-19 vaccines have been highly effective in preventing severe disease in most patients [14,15]. While the vaccination status was only available for 66.5% (n = 998) of patients in the entire study cohort, 37.8% (n = 74) and 43.7% (n = 259) of patients had received at least two vaccine doses in the Delta variant group and the Omicron variant group, respectively. Among patients with known immunization status, the relative rate of those patients who had received at least two vaccine doses was 52.5% in the Delta variant group and 78.7% in the Omicron variant group. By the end of the study period in April 2022, 76.0% of the German population had received at least two COVID-19 vaccine doses [16]. Importantly, a direct comparison between propensity-score matched unvaccinated patients in the wild-type group and the Delta variant group and Omicron variant group, respectively as well as between patients who had received at least two COVID-19 vaccine doses in the Delta variant and the Omicron variant group showed no differences of in-hospital mortality. This finding would suggest that the trend towards a less severe clinical course throughout the pandemic can be attributed to COVID-19 vaccines to a larger extent than to a decreased virulence of novel SARS-CoV-2 variants [17].

Also, since we did only assess whether or not patients had received at least two vaccine doses but not the exact number and

timing of COVID-19 vaccines, this finding may suggest that two vaccine doses may not have been sufficient in those patients with oftentimes multiple comorbidities.

In addition, novel therapeutic agents, and improved knowledge about the clinical management of patients with SARS-CoV-2 infections have likely contributed to a reduction in morbidity and mortality [18–20]. Interestingly, only 26.6% (n = 158) of patients in the Omicron group who were admitted when remdesivir, nirmatrelvir/ritonavir, molnupiravir and monoclonal antibodies were available in the European Union received any of those antiviral treatments. Out of all deceased patients in the Omicron group, only 12.8% (n = 5) received antiviral medication. Those antiviral treatments have mainly demonstrated efficacy in preventing hospitalization if administered during the first days of infection and may not have an effect in patients who are already hospitalized [13]. Notably, the rate of patients receiving additional antibiotic therapy markedly decreased as the expertise in identifying COVID-19 patients with bacterial superinfections requiring antibacterial therapy increased [21].

Finally, the different circulating SARS-CoV-2 variants have distinct phenotypic characteristics which impact patient outcomes. The SARS-CoV-2 Alpha variant was associated with an increased risk of mortality compared to infections with the wild-type virus [22,23]. Later, the SARS-CoV-2 Delta variant has been shown to cause a surge in severe cases and deaths compared to the Alpha variant [24]. In contrast, infections with the SARS-CoV-2 Omicron variant have been associated with reduced morbidity and mortality compared to the Delta variant [25,26]. While the observed marked decrease in severe COVID-19 cases gives reason for optimism regarding the severity in future patients hospitalized with SARS-CoV-2 infections that is comparable to other endemic viral infections, other results of our study account for persistent concern. Firstly, the absolute number of hospitalized patients with SARS-CoV-2 infections in the Omicron group was higher than ever before. However, SARS-CoV-2 infections were certainly not the sole reason for hospitalization in all patients and there are ongoing discussions on how to differentiate patients hospitalized "with SARS-CoV-2″ or "for COVID-19″. It is not possible to retrospectively make this distinction for often multimorbid patients, in whom SARS-CoV-2 can exacerbate underlying conditions.

Regardless, the need for isolation of patients with SARS-CoV-2 infections to prevent nosocomial infections of vulnerable patients and healthcare workers resulted in continuous strain on our healthcare system and in some cases the isolation regulations complicated the discharge of patients or even optimal patient care. The increasing rate of nosocomial SARS-CoV-2 infections in the Omicron variant group shows that despite strict admission screening of all patients and regular RT-PCR testing of all healthcare workers, nosocomial SARS-CoV-2 transmission cannot be reliably prevented in the context of high community transmission and that infection control interventions are persistently required to protect defined vulnerable patient groups. Aside from the absolute and relative increase in nosocomial SARS-CoV-2 infections, also the number of community-acquired SARS-CoV-2 infections among admitted patients increased.

In the future, novel SARS-CoV-2 variants will likely emerge, and it is not guaranteed that those variants will have a similarly diminished severity. To overcome potential immune evasion, COVID-19 vaccines will be adapted to those novel variants. It will therefore be crucial to timely detect and characterize novel SARS-CoV-2 variants and clinical outcomes of infected patients. The in-hospital mortality among COVID-19 patients at our center in the Omicron group was comparable to the in-hospital mortality of patients with seasonal influenza [7,27]. However, it remains to be seen how the co-circulation of SARS-CoV-2 and other endemic viruses will affect epidemiology and patient outcomes in the future.

Our study has important limitations, which are mainly inherent to the retrospective single-center study design. First, the monocentric study character may limit generalizability to other clinical settings. However, important and granular information can be gained from this approach since we compare patients hospitalized in the same clinical setting and thereby achieve a level of comparability. Second, we are only able to determine in-hospital morbidity and mortality but did not assess long-term clinical outcomes after discharge. Third, SARS-CoV-2 variant sequencing was not available for all patients, so they were assigned to whatever SARS-CoV-2 variant was predominantly circulating in Germany during the respective date of infection. Fourth, while COVID-19 vaccinations have had a substantial impact on the clinical course and were responsible for a decline in SARS-CoV-2-related morbidity and mortality worldwide, overall vaccination status were not available or assessed for all patients in our study cohort, especially in the Alpha, Delta, and Omicron variant groups.

Conclusion

In conclusion, in-hospital mortality among hospitalized patients with SARS-CoV-2 infections steadily decreased over the course of the COVID-19 pandemic. This reduction in morbidity and mortality can be attributed to the effect of COVID-19 vaccines, improved clinical management, novel therapeutic agents, and less pathogenic SARS-CoV-2 variants. However, the increasing rate of nosocomial SARS-CoV-2 infections in the Omicron variant group and the practically unchanged duration of hospitalization demonstrate the persistent burden of COVID-19 on the healthcare system.

Ethics approval and consent to participate

The study was reviewed and approved by the Ethics Committee of the Medical Council of Hamburg (WF-052/20). Informed consent was waived due to the retrospective nature of the study.

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CRediT authorship contribution statement

T.T.B., A.H., M.F., S.K., and J.S.z.W. conceived and planned the study. T.T.B. and A.H. wrote the main manuscript text with input from all authors. T.T.B. and A.H. performed statistical analyses and designed the figures. S.K. and J.S.z.W. supervised the project. All authors reviewed the manuscript.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.08.010.

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