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ORIGINAL ARTICLE

Experience with sotrovimab treatment of SARS-CoV-2-infected patients in Denmark

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Aims: To evaluate the experience with use of sotrovimab following severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in high-risk groups.

Methods: In a nationwide, population-based cohort study, we identified all individuals treated with sotrovimab ($N = 2933$) and stratified them by 4 high-risk groups: (A) malignant haematological disease, (B) solid organ transplantation, (C) anti-CD20 therapy ≤1 year and (D) other risks. Cox regression analysis was used to calculate hazard ratios for hospitalization, death and associated prognostic factors.

Results: Of 2933 sotrovimab-treated individuals, 83% belonged to high-risk groups (37.6% haematological malignancy, 27.4% solid organ transplantation and 17.5%

treatment with anti-CD20 ≤1 year). Only 17.8% had other risks (11.8% were pregnant, 10.7% primary immunodeficiency, 21.2% other malignancy, 4.3% received anti-CD20 >1 year and 52.0% other/unknown causes). Within 90 days of infusion, 30.2% were hospitalized and 5.3% died. The main prognostic factors were the predefined high-risk groups, mainly malignant haematological disease and age ≥65 years. Number of COVID-19 vaccines (≥3) was associated with a decreased risk of hospitalization. The Delta but not the Omicron BA.2 variant was associated with a higher risk of death compared to the BA.1 variant.

Conclusion: More than 90% of the patients treated with sotrovimab belonged to the very high-risk groups as described in the Danish guidelines. Sotrovimab-treated individuals remained at a high risk of hospitalization and death which was strongly associated with the underlying immunocompromised state and age. Having received >3 COVID-19 vaccines was association with decreased risk of death and hospitalization.

KEYWORDS
COVID-19, mAB, SARS-CoV-2, SARS-CoV-2 vaccines, sotrovimab

1 | INTRODUCTION

Immunocompromised patients are at increased risk for hospitalization, progression to severe disease and death due to coronavirus disease (COVID-19).[1–5] These risks relative to immunocompetent individuals persist despite COVID-19 immunization.[6,7] In Denmark, immunocompromised individuals are recommended a fourth vaccine dose 6 months after the third vaccination.[8]

Sotrovimab is a monoclonal antibody (mAb) designed to prevent progression of COVID-19 by targeting the highly conserved nonreceptor binding motif (RBM) epitopes that are shared across many sarbecoviruses resulting in neutralization of the virus.[9] In a randomized, placebo-controlled clinical trial (COMET-ICE) among nonhospitalized unvaccinated individuals with mild–moderate COVID-19, sotrovimab demonstrated therapeutic efficacy yielding a 89% risk reduction relative to placebo for the composite endpoint of hospitalization or death.[5,10] However, immunocompromised patients, who might benefit the most from this therapy and for whom the number needed to be treated might be lower were excluded from this trial.

With the emergence of virus variants, there are increasing levels of resistance towards sotrovimab and other mAb.[11–13] For example, in previous in vitro-based studies, sotrovimab neutralized the Delta and Omicron BA.1 SARS-CoV-2 variants,[14] but had reduced neutralization of the Omicron BA.2, BA.4 and BA.5 variants.[13] Additionally, recent data suggest that treatment with mAb may drive resistance in immunocompromised patients.[15]

Sotrovimab has been used for high-risk populations in Denmark since its release for regular use in September 2021 until 7 April 2022, where the use was no longer recommended based on loss of neutralizing capacity on the dominating circulating SARS-CoV-2 variants.[16] In this period, an immense logistic setup to screen and prioritize the high-risk patients for whom sotrovimab was indicated was needed. Furthermore, in some periods, the demand exceeded the supply of the drug and the available resources. Hence, it is important to evaluate the use of the different mAb (here sotrovimab) during the

What is already known about this subject

- In the COMET-ICE randomized controlled trial among nonhospitalized, nonimmunocompromised individuals with mild–moderate COVID-19, sotrovimab demonstrated therapeutic efficacy yielding a 89% risk reduction relative to placebo for the composite endpoint of hospitalization/death.
- Real-world data on the experience with sotrovimab for immunocompromised patients during different waves of the pandemic are scarce.

What this study adds

- Sotrovimab-treated individuals remained at high risk of hospitalization and death which was strongly associated with the immunocompromised state and age.
- Receiving ≥3 vaccines was association with decreased risk of death and hospitalization.
- Risk of death was lower for individuals treated in 2022 than in 2021.
- The Delta but not the Omicron BA.2 variant was associated with a higher risk of death compared to the BA.1 variant.

different waves of the pandemic and moreover evaluate whether the cost and logistics as well as risks associated with the use of this drug outweigh the benefits.

In this study, we summarized the Danish experience with use of sotrovimab following SARS-CoV-2 infection in high- and very high-risk groups defined as patients with: (i) haematological malignancy; (ii) solid organ transplantation (SOT); (iii) nonhaematological malignancy who received B-cell depleting therapy ≤1 year; and (iv) patients individually deemed to be at high risk (i.e., *other risks*). Among these 4 high-risk groups, we evaluated the risk of hospitalization and death within 90 days following treatment with sotrovimab and associated prognostic factors.

2 | METHODS

2.1 | Study design

We used a nationwide, population-based cohort study to evaluate the experience with the use of sotrovimab in high-risk groups in Denmark.

2.2 | Settings

As of 1 July 2022, Denmark had a population of almost 6 million.[17] The health care in Denmark is tax-supported and vaccination, testing and treatment for SARS-CoV-2 is provided free-of-charge. Based on recommendations at the time of the study, all Danish individuals (≥18 years) are offered 3 COVID-19 vaccine doses. By the end of February 2022, immunocompromised patients were offered a subsequent booster after 6 months (~fourth vaccination).[8] By 1 July 2022, 4.30 (90.6%), 4.26 (89.8%) and 3.64 (76.8%) million individuals (≥18 years) living in Denmark had been vaccinated once, twice and thrice, respectively,[18] and 39 347 (0.8% of the adult population) have been vaccinated 4 times. As of 1 July 2022, 50% of the Danish population had tested positive for SARS-CoV-2. In Denmark, the Delta variant was the dominant strain from summer 2021 and in 2022, the Omicron became the dominant variant.[19]

In Denmark, sotrovimab was authorized as therapy following a positive SARS-CoV-2 polymerase chain reaction test based on a pharyngeal swab for individuals with mild to moderate COVID-19 and whom were at high or very high-risk according to national guidelines.[20] Sotrovimab was released for regular use after its authorization in early September 2021. The indication to treat with sotrovimab was defined as the presence of at least 1 high or very high-risk factor; however, due to a shortage of the medication during the period, the indication for its use was further limited to the following very high-risk groups: (i) malignant haematologic disease; (ii) SOT; and/or (iii) treatment with B-cell depleting therapy ≤1 year for nonmalignant haematological diseases (cluster of differentiation (CD20) inhibitors 20 (i.e., anti-CD20 therapy; see Appendix S1 for diagnostic codes and ACT codes). For a smaller group who did not belong to the other very high-risk group but was deemed to be at high risk (e.g., primary immunodeficiency with humoral deficiency, treatment with heavy immunosuppressive drugs affecting the humoral response and pregnancy, for whom vaccination was initially not recommended), an individual decision to treat could be done based on conference discussions. This group (iv) is defined as *other risks* in this paper.

2.3 | Data sources

We used the unique 10-digit personal identification number assigned to all individuals in Denmark at birth or upon immigration to track individuals in *the Danish Civil Registration System*,[21] *the Danish National Hospital Registry (DNHR)*,[22–24] *the Danish Vaccination Registry*[25] and the national COVID-19 surveillance system[26] (further described in Appendix S1). From DNHR, we extracted data on malignant haematological diseases, SOT and other risks. Data on the use of hospital medicine (i.e., sotrovimab and anti-CD20) were provided from each of the 5 regions in Denmark. Information on SARS-CoV-2 variants was obtained from the Danish COVID-19 Genome Consortium (www.covid19genomics.dk) that is responsible for conducting whole genome sequencing of a large proportion of positive cases.

2.4 | Study period

The study period was 6 September 2021–1 July 2022.

2.5 | Study population

We included all individuals treated with sotrovimab following a positive SARS-CoV-2 test in Denmark.

2.6 | High- and very high-risk groups

The study population was further divided in 4 groups according to the disease that led to administration of sotrovimab: (i) malignant haematological disease; (ii) SOT; (iii) anti-CD20 therapy ≤1 year ago for nonmalignant haematological diseases; and (iv) other risks. Study inclusion was date of sotrovimab.

2.7 | Outcomes

Outcomes were calculated as time to the following events:

2.7.1 | Date of first hospitalization ≥24 h

First date an individual was hospitalized irrespective of diagnosis ≥24 h and >24 h after sotrovimab administration (to exclude potential hospitalizations for sotrovimab administration).

2.7.2 | Date of death

Date of death as registered in DCRS irrespective of cause of death.

2.8 | Statistical analyses

In time to death analyses, time was calculated from date of study inclusion until date of death, emigration, loss to follow-up, 1 July 2022 or 90 days after first dosage of sotrovimab, whichever occurred first. In analyses of time to first hospitalization after sotrovimab, time was calculated from latest of date of study inclusion or date of discharge from the hospital until date of hospitalization for >24 h, death, emigration, loss to follow-up, 1 July 2022 or 90 days after first dosage of sotrovimab, whichever occurred first.

For all patients treated with sotrovimab as well as the individual high-risk groups, we used Cox regression analysis to calculate hazard ratios (HR) for hospitalization and death and estimated associated prognostic factors. The following prognostic factors were estimated in univariate and multivariate models including all the following factors: risk category, sex (female/male), age (</≥ 65 years), number of vaccinations at baseline (<2, 2, 3 or 4), calendar year at baseline (2021 or 2022), variant subtype (Delta, Omicron BA.1 and BA.2) and time from a positive test for SARS-CoV2 to administration of sotrovimab (≤/> 3 days). Cumulative incidence functions were used to illustrate time to the outcome concerning all prognostic factors as described above, using time after sotrovimab as the time scale. In sensitivity analyses of hospitalization, all patients admitted for >24 h at time of sotrovimab therapy were excluded from the analyses.

Data were analysed using STATA 14 statistical software.

2.9 | Ethical considerations

This study was performed as a national surveillance study under the authority task of the Danish national infectious disease control institute, Statens Serum Institut. The study was approved by The Danish Data Protection Agency (permission no. 21/04383). According to Danish regulations, national surveillance activities, as well as studies solely relying on register information, do not require individual consent nor approval from an ethics committee.

2.10 | Role of the funding source

This study did not receive funding and, as such, funding did not play a role in collecting, analysing or interpreting data, nor in writing the report.

3 | RESULTS

We identified 2933 patients who fulfilled the inclusion criteria (37.6% haematological malignancy, 27.4% SOT, 17.5% with no haematological malignancy who had received anti-CD20 therapy ≤1 year ago and 17.6% with other risks of whom 11.8% were pregnancy, 10.7% had primary immunodeficiency, 21.2% had other malignancy and 4.3% had receive anti-CD20 therapy >1 year ago). Of these, the SARS-CoV-2 variant subtype was as following: Delta: 289, Omicron BA.1: 381 and Omicron BA.2: 1573. For 690 patients, the variant type was unknown, as samples had not been sequenced. The median time to sotrovimab therapy was 2 days from a positive test (interquartile range; IQR: 1–4). In total, 21.3% were hospitalized for ≥24 h at time of sotrovimab administration (27.7% haematological malignancy, 11.6% SOT, 8.0% with no haematological malignancy who had received anti-CD20 therapy ≤1 year ago and 36.1% of patients with other risks). A further distribution of patients and diagnoses within the subgroups are shown in Appendix S1 (Table 1x). The median age was 59.0 years (IQR: 44.5–72.0; 39.0% ≥65 years), with the highest age among patients with haematological malignancy (median: 70.0; IQR: 58.8–76.7; 62.8% ≥65 years) and the lowest age among patients treated with anti-CD20 therapy (median: 47.6; IQR: 39.5–58.1; 14.0% ≥65 years). Overall, 50.4% of the patients were male with the highest fraction being males among patients with haematological malignancy (58.9%) and the lowest fraction among patients treated with anti-CD20 therapy (30.9%). Almost 95% of all patients treated with sotrovimab and more than 89.5% of all high-risk groups were born in Denmark. In the overall population, 16.4% of all patients treated with sotrovimab had a Charlson comorbidity index score of 0, ranging from 0% among those with haematological malignancy to 46.9 and 36.4% among patients treated with anti-CD20 therapy ≤1 year ago and patients with other risks. The majority of sotrovimab-treated patients (63.4%) including those with haematological malignancy, SOT and anti-CD20 therapy had in total received 3 COVID-19 vaccine doses at the time of sotrovimab therapy (63.8, 69.0 and 74.3%, respectively), whereas this was only the case for 42.7% of patients with other risks. Among patients with other risks, 35.2% had received ≤1 vaccine (pregnancy: 80.0%, immunodeficiency: 0.1%, other cancer: 20.2% and other/not known: 39.0%).

The study included 696 person-years of follow-up for all patients treated with sotrovimab and during this time, 30.2% were hospitalized and 5.3% died due to any cause (Table 1). Two patients were not Danish residents and were therefore excluded from the following analysis due to lack of follow-up.

3.1 | Risk of hospitalization after sotrovimab and associated prognostic factors

In both univariate and multivariate models, risk of hospitalization after treatment with sotrovimab was highly associated with the specific (very) high-risk groups (Figure 1A, Table 2) with the highest risk among patients with underlying haematological malignancy followed by other risks, SOT and anti-CD20 therapy (SOT: adjusted [a]HR: 0.61 [95%CI: 0.51–0.74]; anti-CD20: 0.31 [0.24–0.41]; other risks: 0.74 [0.60–0.92] compared to haematological malignancy). The risk of

TABLE 1 Baseline characteristics and outcomes during follow-up

	Treated with sotrovimab, all risk groups	Haematological malignancy	SOT	Anti-CD-20 therapy ≤1 year (nonhaematological malignancy)	Other risks
Number (%)	2933	1104 (37.6)	800 (27.4)	514 (17.5)	515 (17.6)
Age, median (IQR) years	59.0 (44.5–72.0)	70.0 (58.8–76.7)	53.0 (41.6–64.0)	47.6 (39.5–58.1)	55.9 (37.1–73.4)
<18 years, *n* (%)	41 (1.4)	11 (1.0)	20 (2.5)	6 (1.1)	4 (0.8)
≥65 years, *n* (%)	1144 (39.0)	693 (62.8)	184 (23.0)	72 (14.0)	195 (37.9)
Male, *n* (%)	1477 (50.4)	650 (58.9)	454 (56.8)	159 (30.9)	214 (41.6)
Female, *n* (%)	1456 (49.6)	454 (41.1)	346 (43.3)	355 (69.1)	301 (58.5)
Country of origin, Denmark, *n* (%)	2771 (94.5)	1061 (96.1)	754 (94.3)	493 (95.9)	463 (89.9)
Distribution of other:					
Pregnant, *n* (%)					61 (11.8)
Primary immunodeficiency, *n* (%)					55 (10.7)
Other malignancy, *n* (%)					109 (21.2)
Anti-CD20 >1 year ago, *n* (%)					22 (4.3)
Other/not known, *n* (%)					268 (52.0)
Distribution of anti-CD20 therapy:					
Rituximab, *n* (%)				256 (49.8)	
Ocrelizumab, *n* (%)				162 (31.5)	
Rituximab and Ocrelizumab, *n* (%)				10 (1.9)	
Other/unknown, *n* (%)				86 (16.7)	
Charlson comorbidity score index: *n* (%)					
Low (score = 0)	482 (16.4)	0 (0)	51 (6.4)	243 (47.3)	188 (36.5)
Medium (score = 1–2)	1112 (37.9)	425 (38.5)	319 (39.9)	199 (38.7)	169 (32.8)
High (score >2)	1339 (45.7)	679 (61.5)	430 (53.8)	72 (14.0)	158 (30.7)
COVID-19 vaccines: *n* (%)					
≤1	267 (9.1)	44 (4.0)	26 (3.3)	16 (3.1)	181 (35.2)
2	309 (10.5)	111 (10.1)	60 (7.5)	50 (9.7)	88 (17.1)
3	1858 (63.4)	704 (63.8)	552 (69.0)	382 (74.3)	220 (42.7)
≥4	499 (17.0)	245 (22.2)	162 (20.3)	66 (12.8)	26 (5.1)
Sotrovimab therapy:					
Sotrovimab before 3 days, *n* (%)	893 (30.5)	343 (31.1)	184 (23.0)	190 (37.0)	176 (34.2)
Time to sotrovimab median days (IQR)	2 (1–4)	2 (1–4)	2 (1–3)	3 (2–5)	2 (1–5)
Time to sotrovimab for those receiving it after >3 days, median days (IQR)	6 (4–14)	6 (4–16)	5 (4–12.5)	6 (4–20)	6 (5–9)
Received sotrovimab during admission, *n* (%)	626 (21.3)	306 (27.7)	93 (11.6)	41 (8.0)	186 (36.1)
Received sotrovimab as outpatient, *n* (%)	2307 (78.7)	798 (72.3)	707 (88.4)	473 (92.0)	329 (63.9)
Follow-up:					
Hospitalization ≥24 h within 90 days of COVID-19 diagnosis, *n* (%)	813 (27.7)	398 (36.1)	183 (22.9)	61 (11.9)	171 (33.2)
All-cause death within 90 days of COVID-19 diagnosis, *n* (%)	156 (5.3)	96 (8.7)	9 (1.8)	6 (1.2)	45 (8.7)
Total person-years of follow-up (PYR)	696	257	196	124	119

Abbreviations: IQR, interquartile range; PYR, person years of follow up; SOT, solid organ transplantation.

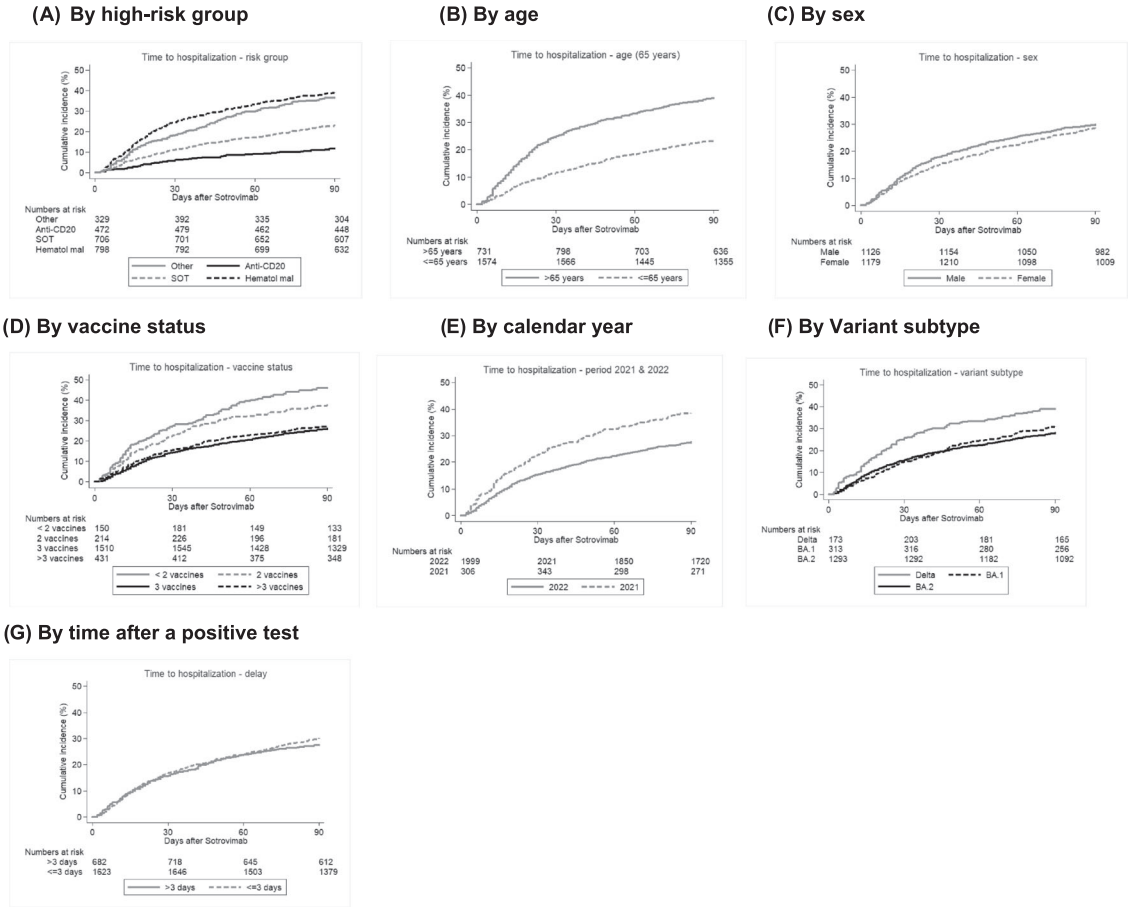

FIGURE 1 Risk of hospitalization: (A) by high-risk group, (B) by age, (C) by sex, (D) by SARS-CoV-2 vaccine status, (E) by calendar year, (F) by variant subtype and (G) by time after a positive test

hospitalization was further strongly associated with age ≥65 years (*vs.* <65 years; aHR: 1.87 [1.63–2.15]), vaccine status (3 vaccine doses: 0.50 [0.39–0.64] and ≥4 vaccine doses: 0.46 [0.34–0.62] compared to <2 vaccine doses]. We observed no substantial association with sex or delay in time from SARS-CoV-2 test to administration of sotrovimab (>3 vs ≤3 days). In the univariate model, we observed a lower risk of hospitalization in 2022 compared to 2021 (Figure 1B–G). In the stratified analyses, the risk of hospitalization in the high-risk groups anti-CD20 therapy and other risks was considerably lower in 2022 compared to 2021 irrespective of adjustment (Table 2, Figure 1). Excluding individuals who were hospitalized for >24 h at time of sotrovimab administration did not change the overall findings substantially. (Table 2x, Figure 2x in Appendix S1).

In a subgroup analysis, in which only individuals with an assigned variant subtype were analysed (2243; 76.5%) patients with the Delta variant had a higher risk of hospitalization compared to those with Omicron BA.1 variant in the univariate analyses; however, no significant difference between the risk of hospitalization was found between the Delta and Omicron BA.1 and BA.2 variants in the multivariate analyses (Table 2).

3.2 | Risk of death and associated prognostic factors

We found a high and almost identical risk of death for the (very) high-risk groups haematological malignancy and other risks, whereas a lower risk was observed in the SOT and anti-CD20 therapy groups (Figure 2A, Table 3). Compared to haematological malignancy, relative risks of death were: SOT: aHR: 0.26 (95%CI: 0.13–0.51); anti-CD20: 0.36 (0.15–0.83); other risks: 0.88 (0.58–1.33).

In the univariate and multivariate models, risk of death was further associated with male sex (female *vs.* male: aHR: 0.68; 95% CI: 0.49–0.95), age ≥65 years (7.11 [4.54–11.14]), vaccine status (3 vaccine doses: 0.37 [0.22–0.62] and ≥4 vaccine doses: 0.26 [0.13–0.53] compared to <2 vaccine doses), and calendar year (2022: 0.64; 0.44–0.95), whereas we observed no strong association with delay in time to sotrovimab treatment (>3 *vs.* ≤3 days). Due to a potential interaction, we stratified the analyses on high-risk groups. Although the association of certain risk factors changed slightly and became more imprecise due to decreased statistical power, the associations observed in the stratified analyses did not differ substantially from the associations found in

TABLE 2 Prognostic factors for hospitalization among sotrovimab treated SARS-CoV-2-positive patients

	Treated with sotrovimab, all risk groups (*n*: 2933) (*n* with event: 813)		Haematological malignancy (*n*: 1104) (*n* with event: 398)		SOT (*n*: 800) (*n* with event: 183)	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
High-risk group						
Haematological malignancy	Ref (1)	Ref (1)	-	-	-	-
SOT	0.53 (0.44–0.63)	0.61 (0.51–0.74)	-	-	-	-
Anti-CD-20	0.26 (0.20–0.34)	0.31 (0.24–0.41)	-	-	-	-
Other risks	0.91 (0.76–1.08)	0.74 (0.60–0.92)	-	-	-	-
Sex						
Male	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
Female	0.94 (0.81–1.07)	1.03 (0.90–1.19)	0.88 (0.72–1.08)	0.84 (0.69–1.03)	1.23 (0.92–1.64)	1.24 (0.93–1.66)
Age						
<65 years	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
≥65 years	1.87 (1.63–2.15)	1.58 (1.36–1.83)	1.29 (1.05–1.59)	1.61 (1.30–2.00)	1.40 (1.01–1.93)	1.35 (0.96–1.89)
Vaccination status						
<2	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
2	0.78 (0.59–1.02)	0.82 (0.62–1.08)	0.87 (0.55–1.38)	0.83 (0.52–1.33)	0.87 (0.33–2.28)	0.88 (0.34–2.33)
3	0.49 (0.40–0.61)	0.50 (0.39–0.64)	0.40 (0.27–0.61)	0.33 (0.22–0.50)	0.86 (0.38–1.96)	0.86 (0.38–1.96)
≥4	0.53 (0.41–0.68)	0.46 (0.34–0.62)	0.35 (0.22–0.55)	0.27 (0.17–0.42)	1.13 (0.48–2.65)	1.08 (0.45–2.57)
Calendar year						
2021	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
2022	0.67 (0.56–0.79)	0.86 (0.71–1.04)	0.84 (0.63–1.12)	1.15 (0.84–1.55)	0.93 (0.62–1.38)	0.87 (0.58–1.32)
Time of sotrovimab, days after a positive test						
≤3 days	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
>3 days	0.91 (0.78–1.06)	0.87 (0.75–1.02)	0.74 (0.59–0.93)	0.71 (0.57–0.89)	0.96 (0.67–1.36)	0.97 (0.68–1.38)
Variant subtype						
Delta						
Omicron BA.1						
Omicron BA.2						

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; SOT, solid organ transplantation.

TABLE 2 (Continued)

	Anti-CD20 therapy ≤1 year (nonhaematological malignancy) (*n*: 514) (*n* with event: 61)		Other risks (*n*: 515) (*n* with event: 171)		SUBGROUP ANALYSIS: Treated with sotrovimab, all risk groups with variant subtype: 2243 (*n* with event: 30 (Delta), 39 (BA.1) and 56 (BA.2)	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
High-risk group						
Haematological malignancy	-	-	-	-	-	Ref (1)
SOT	-	-	-	-	-	0.68 (0.56–0.84)
Anti-CD-20	-	-	-	-	-	0.34 (0.25–0.47)
Other risks	-	-	-	-	-	0.86 (0.68–1.09)
Sex						
Male	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	Ref (1)
Female	1.37 (0.76–2.45)	1.31 (0.73–2.36)	1.19 (0.87–1.62)	1.24 (0.90–1.71)	-	0.99 (0.84–1.16)
Age						
<65 years	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	Ref (1)
≥65 years	1.75 (0.93–3.29)	2.09 (1.10–3.99)	1.82 (1.35–2.46)	2.08 (1.53–2.84)	-	1.63 (1.37–1.94)
Vaccination status						
<2	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	Ref (1)
2	0.19 (0.03–1.11)	0.15 (0.02–0.91)	0.83 (0.55–1.26)	0.85 (0.56–1.30)	-	0.87 (0.63–1.21)
3	0.65 (0.20–2.07)	0.74 (0.23–2.40)	0.53 (0.38–0.75)	0.63 (0.43–0.94)	-	0.55 (0.41–0.74)
≥4	0.36 (0.09–1.50)	0.40 (0.09–1.67)	0.66 (0.33–1.33)	0.83 (0.40–1.73)	-	0.45 (0.32–0.65)
Calendar year						
2021	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	-
2022	0.42 (0.21–0.85)	0.32 (0.15–0.66)	0.56 (0.42–0.76)	0.68 (0.47–0.98)	-	-
Time of sotrovimab, days after a positive test						
≤3 days	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	Ref (1)
>3 days	1.06 (0.63–1.78)	1.01 (0.60–1.71)	1.22 (0.90–1.66)	1.17 (0.85–1.62)	-	0.84 (0.70–1.00)
Variant subtype						
Delta					1.52 (1.22–1.89)	1.14 (0.90–1.45)
Omicron BA.1					1.10 (0.90–1.36)	1.04 (0.84–1.29)
Omicron BA.2					Ref (1)	Ref (1)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; SOT, solid organ transplantation.

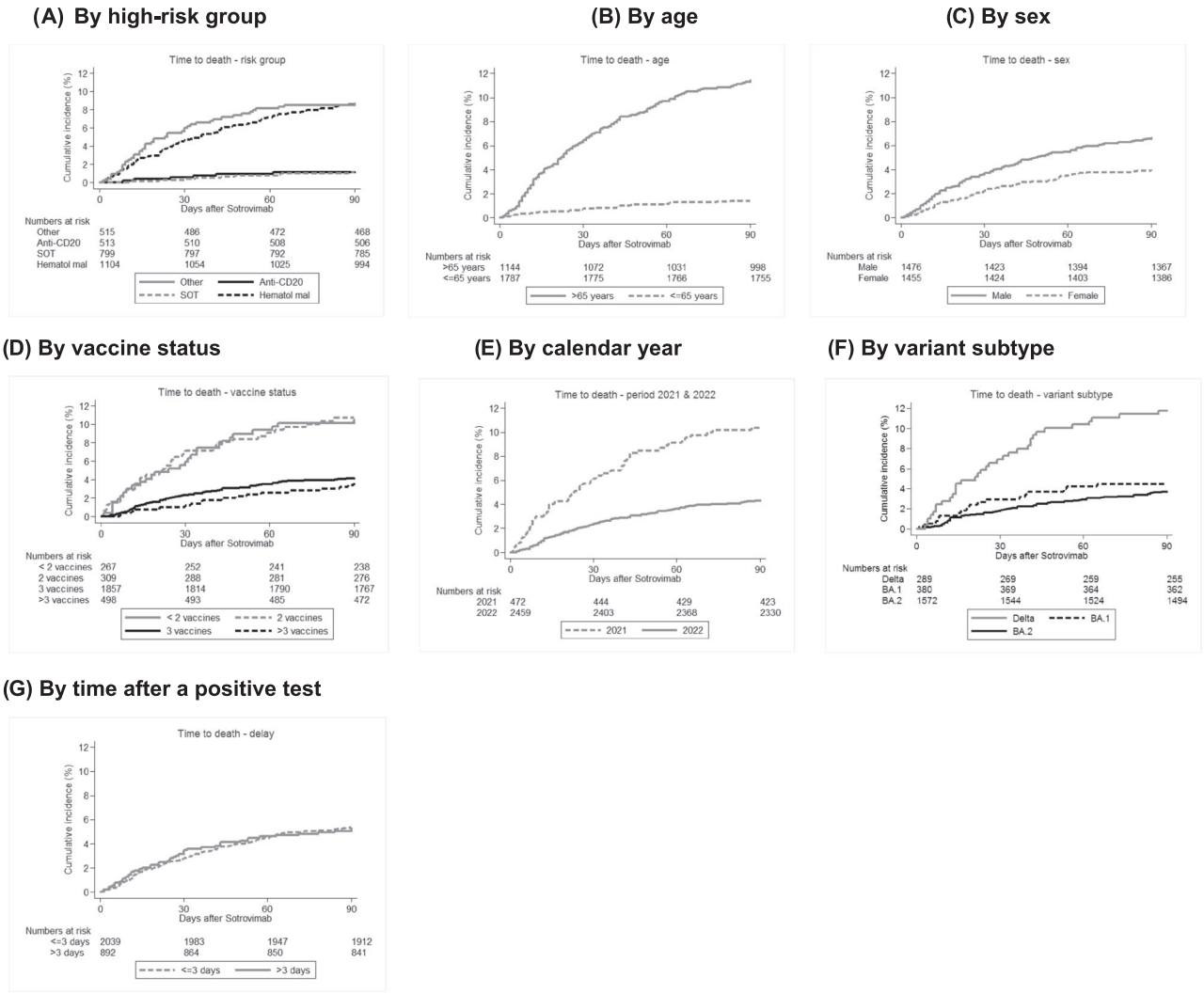

FIGURE 2 Risk of death: (A) by high-risk group, (B) by age, (C) by sex, (D) by SARS-CoV-2 vaccine status, (E) by calendar year, (F) by variant subtype and (G) by time after a positive test

the overall analyses, an exception was that delay in time to sotrovimab in the SOT group was associated with risk of death (4.88; 1.27–18.73).

In the subgroup analysis of individuals with variant information, individuals with the Delta variant had a higher risk of death compared to individuals with the Omicron BA.1 variant (aHR: 1.71 [1.05–2.80]), whereas no difference in risk of death was found between the Omicron BA.2 and BA.1 variants (aHR: 1.04 [0.59–1.83]; Table 3).

4 | DISCUSSION

In this nationwide, population-based cohort study of 2933 SARS-CoV-2 polymerase chain reaction positive patients treated with sotrovimab, 83.4% belonged to very high-risk groups as defined in the Danish guidelines and only 17.8% belonged to the high-risk group other risks. Sotrovimab therapy was given within a median time of 2 days (IQR: 1–4) of a positive test. Among sotrovimab-treated individuals, 30.2% were hospitalized and 5.3% died from any cause within the initial 90 days after treatment. The main prognostic factors for an increased risk of hospitalization and death were the predefined high-risk groups, especially haematological malignancy and age ≥65 years, whereas risk of these outcomes was decreased in individuals who had been vaccinated ≥3 times. For death, a protective effect was further observed in association with especially calendar time (2022 *vs*. 2021). In line with that, the Delta variant was associated with a 1.7-fold higher risk of death compared to the Omicron BA.1 variant, whereas no difference in risk was observed between the Omicron BA.1 and BA.2 variants.

To our knowledge, this is the largest study summarizing and describing risk factors for hospitalization and death after sotrovimab therapy during both the Delta and Omicron periods among 4 high-risk groups of largely immunosuppressed patients.

With this study, we summarized the Danish experience with the use of sotrovimab following SARS-CoV-2 infection and found that the

TABLE 3 Prognostic factors for death among sotrovimab-treated SARS-CoV-2-positive patients

	Treated with sotrovimab, all risk groups (*n*: 2933) (*n* with event: 156)		Haematological malignancy (*n*: 1104) (*n* with event: 96)		SOT (*n*: 514) (*n* with event: 9)	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Disease category						
Haematological malignancy	Ref (1)	Ref (1)	-	-	-	-
SOT	0.12 (0.06–0.25)	0.26 (0.13–0.51)	-	-	-	-
Anti-CD-20	0.13 (0.06–0.30)	0.36 (0.15–0.83)	-	-	-	-
Other risks	1.01 (0.71–1.45)	0.88 (0.58–1.33)	-	-	-	-
Sex						
Male	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
Female	0.59 (0.43–0.82)	0.68 (0.49–0.95)	0.93 (0.62–1.40)	0.91 (0.60–1.37)	0.37 (0.08–1.80)	0.35 (0.07–1.75)
Age						
<65 years	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
≥65 years	8.63 (5.62–13.23)	7.11 (4.54–11.14)	3.97 (2.21–7.13)	4.89 (2.69–8.89)	2.68 (0.72–9.99)	2.09 (0.53–8.30)
Vaccination status						
<2	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
2	1.02 (0.62–1.68)	0.99 (0.58–1.68)	1.79 (0.67–4.74)	1.28 (0.48–3.45)	NA	NA
3	0.38 (0.25–0.59)	0.37 (0.22–0.62)	0.73 (0.29–1.82)	0.50 (0.20–1.26)	0.14 (0.01–1.30)	0.12 (0.01–1.21)
≥4	0.33 (0.18–0.60)	0.26 (0.13–0.53)	0.42 (0.15–1.20)	0.31 (0.11–0.90)	0.78 (0.09–6.71)	0.65 (0.07–6.48)
Calendar year						
2021	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
2022	0.40 (0.29–0.57)	0.64 (0.44–0.95)	0.34 (0.22–0.52)	0.49 (0.30–0.79)	1.41 (0.18–11.25)	0.62 (0.06–6.05)
Time of sotrovimab, days after a positive test						
≤3 days	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)	Ref (1)
>3 days	0.99 (0.70–1.39)	0.86 (0.61–1.22)	1.02 (0.66–1.57)	0.89 (0.58–1.38)	4.24 (1.14–15.77)	4.88 (1.27–18.73)
Variant subtype						
Delta						
Omicron BA.1						
Omicron BA.2						

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; SOT, solid organ transplantation.

TABLE 3 (Continued)

	Anti-CD-20 therapy ≤1 year (nonhaematological malignancy) (*n*: 515) (*n* with event: 6)		Other risks (*n* with event: 45)		SUBGROUP ANALYSIS: Treated with sotrovimab, all risk groups with variant subtype: *n*: 2243 (*n* with event: 10 (delta), 10 (BA.1) and 12 (BA.2)	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Disease category						
Haematological malignancy	-	-	-	-	-	Ref (1)
SOT	-	-	-	-	-	0.27 (0.11–0.63)
Anti-CD-20	-	-	-	-	-	0.44 (0.17–1.12)
Other risks	-	-	-	-	-	1.08 (0.67–1.75)
Sex						
Male	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	
Female	0.44 (0.09–2.19)	1.05 (0.17–6.47)	0.34 (0.18–0.64)	0.40 (0.21–0.76)	-	0.68 (0.46–1.02)
Age						
<65 years	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	Ref (1)
≥65 years	NA	NA	9.71 (4.33–21.74)	8.47 (3.73–19.24)	-	6.82 (4.02–11.55)
Vaccination status						
<2	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	Ref (1)
2	NA	NA	1.12 (0.56–2.27)	0.85 (0.41–1.79)	-	0.93 (0.50–1.74)
3	NA	NA	0.39 (0.19–0.81)	0.25 (0.12–0.53)	-	0.35 (0.19–0.66)
≥4	NA	NA	NA	NA	-	0.19 (0.08–0.46)
Calendar year						
2021	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	-
2022	0.08 (0.02–0.42)	0.03 (0.00–0.32)	0.82 (0.45–1.52)	1.26 (0.64–2.48)	-	-
Time of sotrovimab, days after a positive test						
≤3 days	Ref (1)	Ref (1)	Ref (1)	Ref (1)	-	
>3 days	0.86 (0.16–4.67)	0.17 (0.02–1.62)	0.53 (0.26–1.08)	0.69 (0.34–1.41)	-	0.80 (0.52–1.22)
Variant subtype						
Delta					3.34 (2.19–5.10)	1,71 (1.05–2.80)
Omicron BA.1					1.22 (0.71–2.10)	1.04 (0.59–1.83)
Omicron BA.2					Ref (1)	Ref (1)

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; SOT, solid organ transplantation.

hospital-based screening and prioritizing had been successful with regard to adhesion to the national treatment guidelines.[20] As many as 82.4% of the patients who had been identified and treated belonged to very high-risk groups, whereas only 17.8% belonged to the high-risk group other risks. In approximately 50% of the other risks group ($N = 269$), the risk factor could not be identified. Nevertheless, this might be due to lack of information on non-anti-CD20 immunosuppressant therapeutics. Lastly, 39.0% of this group ($N = 105$) were insufficiently vaccinated (≤1 vaccine), which might have triggered the decision to treat.

We observed that in patients treated with sotrovimab, the risk of hospitalization and death was high in the subsequent 90 days after a SARS-CoV-2 test and was mainly affected by the underlying high-risk group, as well as well-established risk factors—especially age. Importantly, we found that having received ≥3 COVID-19 vaccine doses was highly associated with reduced risk of hospitalization and death. A similar effect of vaccines has been found in a study of sotrovimab-treated SOT patients by Solera *et al.*[27] As only a minor fraction of the individuals who received sotrovimab had received the fourth vaccination at time of sotrovimab therapy and the time since the fourth vaccine dose is presumed to be short, any strong conclusions regarding an additional benefit of a fourth vaccine dose cannot be made. Results from the general population in England[28] have illustrated less severe outcomes concerning risk of hospitalization and death in association with the Omicron variant compared to the Delta variant. In accordance with these findings, we found that a positive SARS-CoV-2 test in the year of 2022 *vs*. the last 6 months of 2021 (as a surrogate estimate for Omicron and Delta variant) was associated with a trend towards a lower risk of hospitalization and a statistically significant 36% reduction in risk of death for patients treated with sotrovimab. Similar results were observed in a subgroup analysis of 2243 patients for whom we had data on variant type, hence illustrating a lower severity considering risk of death during the Omicron wave. Previous studies have indicated lack of effect of sotrovimab on the Omicron BA.2 variant.[29,30] We cannot elucidate whether sotrovimab had an attenuated effect on the Omicron *vs*. the Delta variant; however, we found no major difference in results of hospitalization or death in association with the 2 Omicron variants BA.1 and BA.2, indicating a similar effect or similar lack of effect for both Omicron variants.

Finally, whereas the COMET-ICE study[5,10] showed effect of early treatment (≤5 days from a positive test) with sotrovimab for high-risk patients, no effect has been shown among hospitalized patients with COVID-19 in the ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) trial.[31] Although both studies excluded immunocompromised patients, the current evidence suggests that sotrovimab should be administered as soon as possible after infection. In Denmark, sotrovimab was given shortly after a positive test as illustrated in our results (Median time to sotrovimab: 2 days (IQR: 1–4)). We did not find any indication that the time to sotrovimab treatment (>3 *vs*. ≤3 days after a positive test) was a prognostic factor for the risk of hospitalization or death other than for risk of hospitalization for patients with haematological malignancy (aHR: 0.71; 95%: 0.57–0.89). In this very high-risk group, 27.7% received the therapy during a current admission; however, excluding these patients did not change the estimates substantially. In the association with time to sotrovimab and risk of death for SOT patients (aHR: 4.88; 95%CI: 1.27–18.73); however, this analysis is based on only 9 patients who died.

Huang *et al.*[32] used real-world data to estimate the effects of sotrovimab and found reduced risk of hospitalization or death (relative risk of hospitalization or death: 0.60; 95%CI: 0.37–1.00), which is in accordance with the findings from the COMET-ICE trial.[3] Nevertheless, studies on immunocompromised patients are scarce. Studies on SOT patients are mainly small[33–35] and only few included a control group for comparison.[27,36,37] Aggarwal *et al.*[36] compared 522 patients who had received sotrovimab (24.9% immunosuppressed) with 9470 untreated during the Delta wave (1 October–11 December 2021), propensity-score matched patients, and found that sotrovimab was associated with a 63% decreased odds of all-cause hospitalization (adjusted odds ratio [aOR]: 0.37; 95%CI: 0.19–0.66) and an 89% decrease in the odds of all-cause mortality (aOR: 0.11; 0.00–0.79). Unfortunately, stratification on the immunocompromised population was not done. In a more recent study from Aggarwal *et al.*[38] based on data from the Omicron BA.1. wave on 1542 sotrovimab-treated patients propensity matched to 3663 untreated patients, no difference in 28-days hospitalization (aOR: 0.82; 95% CI 0.55–1.19) or all-cause 28-day mortality (aOR 0.62; 0.07–2.78) was found. However, in a subgroup analysis including only the 19.5% with mild and the 22.8% with moderate–severe immunosuppression a trend towards a lower risk of hospitalization (OR 0.63, 95% CI 0.38–1.04) was observed. Also with data from the Omicron wave, Piccicacco *et al.*[37] compared the effect of sotrovimab ($N = 82$) in high-risk patients with mild–moderate COVID-19 with a control cohort of high-risk COVID-19 outpatients whom had declined therapy. A major part of the sotrovimab cohort (92%) and the controls (73.3%) where immunocompromised (>70% SOT and < 10% haematology/oncology). This study found that patients who received sotrovimab were less likely to be hospitalized or visit the emergency department within 29 days from symptom onset (OR 0.28; 95%CI: 0.11–0.71). Still, the number of patients was small, hence the use of a composite endpoint. Lastly, Solera *et al.*[27] in a study performed in the Omicron period compared 106 SOT patients treated with sotrovimab with 187 non-matched SOT patients who did not receive sotrovimab and found that sotrovimab was associated with a reduced risk of oxygen requirement (risk ratio: 0.24; 95%CI: 0.1–0.59) and hospitalization within 30 days (risk ratio: 0.58; 95%CI: 0.35–0.94) in univariate analyses. However, risk of hospitalization became insignificant after adjustment for age, type of transplant, number of vaccines and number of comorbidities.

Although our study was much larger than these 3 studies, we could not investigate the effect of sotrovimab due to lack of a sufficiently matched comparison cohort, as patients who had not been offered sotrovimab were younger, less ill, or the patient might have chosen not to get the treatment due to logistical problems or underlying beliefs (i.e., risk of confounding by indication).

Hence, based on current evidence, the effect of sotrovimab in different immunocompromised subgroups needs to be further examined.

For all patients treated with sotrovimab in Denmark, we had access to hospital-based nationwide data from the COVID-19 surveillance program and national registries of a high quality, with information on SARS-CoV-2 tests, vaccination status, hospital diagnosis and vital status. A noteworthy strength is the long follow-up with data from the entire period that sotrovimab was used as well as SARS-CoV-2 variant data for the majority of the cases.

The study had to rely on hospital data for data on sotrovimab, which is why a small fraction of patients might have been missed. Furthermore, we used register-based diagnoses for admissions and diagnostic codes for high-risk groups. Although diagnostic codes may be inaccurate and incomplete, we used all-cause admission and death, and therefore presume that a possible misclassification of outcomes is considered nondifferential why the effect on the estimated relative risks is considered to be negligible. Although many of the conditions in the Charlson comorbidity index might be risk factors for progression of COVID-19, we did not adjust for this factor, as it may be intermediate factor between the risk group and the event. Finally, despite an overall large sample size, the number of events in some of the stratified analysis was small and therefore the estimates had broad confidence intervals.

5 | CONCLUSION

In summary, almost all individuals treated with sotrovimab in Denmark belonged to the risk groups as defined in the Danish guidelines. Despite treatment with sotrovimab, the subsequent risk of hospitalization and death was high and affected by the underlying immunocompromised state and high age (≥65 years), whereas a protective effect was mainly observed in association with the number of COVID-19-vaccine doses (≥3), and calendar time as well as the switch to the Omicron variant. Further studies are needed concerning the effect of sotrovimab.

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COMPETING INTERESTS

Marie Helleberg has participated in a number of advisory boards from the following companies (AstraZeneca, GSK, Jannsen, MSD, and Roche & Sobi).

All other authors declare no competing interests.

CONTRIBUTORS

Conceived the idea for the study and provided methodological input: L.D.R., A.L., A.Ø., B.K.P., H.R.C., H.N., I.S.J., L.H.O., L.W., M.H., M.S., M.D., T.A.R., T.B., T.S.P., Å.B.A., M.A.G., S.M.E., M.S. and N.O. Did the statistical analyses: N.O. Wrote the first draft of the manuscript: L.D.R. Accessed and verified the underlying data for the study: S.M.E., M.S. and N.O. All authors approved the final version and had final responsibility for the decision to submit for publication. All authors had full access to the data and contributed to interpreting the data and writing the manuscript.

DATA AVAILABILITY STATEMENT

Deidentified participant-level data are available for access to members of the scientific and medical community for noncommercial use only. Applications should be submitted to Forskerservice at the Danish Health Data Authority, where they will be reviewed on the basis of relevance and scientific merit. Data are available now, with no defined end date.

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REFERENCES

1. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *Jama*. 2020;323(18):1775-1776. doi:10.1001/jama.2020.4683
2. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759-765. doi:10.15585/mmwr.mm6924e2
3. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature*. 2020;584(7821):430-436. doi:10.1038/s41586-020-2521-4
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama*. 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648
5. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of Sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. *Jama*. 2022;327(13):1236-1246. doi:10.1001/jama.2022.2832
6. Embi PJ, Levy ME, Naleway AL, et al. Effectiveness of 2-dose vaccination with mRNA COVID-19 vaccines against COVID-19-associated hospitalizations among immunocompromised adults - nine states, January–September 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(44):1553-1559. doi:10.15585/mmwr.mm7044e3
7. Deepak P, Kim W, Paley MA, et al. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. *Ann Intern Med*. 2021;174(11):1572-1585. doi:10.7326/M21-1757
8. The Danish Health Authorities S. Anbefalinger vedr. 4. stik covid-19 vaccine til personer med svært nedsat immunforsvar. 2022. Accessed May 18, 2022. https://www.sst.dk/-/media/Udgivelser/2022/Corona/Retningslinjer/Anbefalinger-vedr_-4_-stik-covid-19-vaccine-til-personer-med-svaert-nedsat-immunforsvar.ashx
9. Hansen J, Baum A, Pascal KE, et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science*. 2020;369(6506):1010-1014. doi:10.1126/science.abd0827

10. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody Sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934
11. AstraZenica. Evusheld long-acting antibody combination retains neutralising activity against Omicron variants including BA.2 in new independent studies. 2022. Accessed May 16, 2022. https://www.astrazeneca.com/media-centre/medical-releases/evusheld-long-acting-antibody-combination-retains-neutralising-activity-against-omicron-variants-including-ba2-in-new-independent-studies.html
12. Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat Med*. 2022;28(6):1297-1302. doi:10.1038/s41591-022-01792-5
13. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. *Nature*. 2022;604(7906):553-556. doi:10.1038/s41586-022-04594-4
14. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 omicron antigenic shift. *Nature*. 2022;602(7898):664-670. doi:10.1038/s41586-021-04386-2
15. Destras G, Bal A, Simon B, Lina B, Josset L. Sotrovimab drives SARS-CoV-2 omicron variant evolution in immunocompromised patients. *Lancet Microbe*. 2022;3(8):e559. doi:10.1016/S2666-5247(22)00120-3
16. Statens Serum Institut S. Now, an Omicron variant, BA.2, accounts for almost half of all Danish Omicron-cases. 2022. https://en.ssi.dk/news/news/2022/omicron-variant-ba2-accounts-for-almost-half-of-all-danish-omicron-cases
17. https://www.dst.dk/en/Statistik/emner/borgere/befolkning/befolkningstal (accessed 02.05.2022 2022).
18. (SST) S. Covid-19 surveillance. Current data on the development of coronavirus in Denmark. 2022.
19. Gram MA, Emborg HD, Schelde AB, et al. Vaccine effectiveness against SARS-CoV-2 infection or COVID-19 hospitalization with the alpha, Delta, or omicron SARS-CoV-2 variant: a nationwide Danish cohort study. *PLoS Med*. 2022;19(9):e1003992. doi:10.1371/journal.pmed.1003992
20. *Retningslinje til behandling af voksne patienter med COVID-19*. The Danish Infectious Disease Society (DSI). https://www.infmed.dk/site/tools/download.php?UID=60119911ec6a89f8d9d6d3442a5a6830b4b3b1be2022)
21. Frank L. Epidemiology. When an entire country is a cohort. *Science*. 2000;287(5462):2398-2399. doi:10.1126/science.287.5462.2398
22. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3):263-268.
23. WHO WHO. International statistical classification of diseases and related health problems. 2011. p. 1–201.
24. (Sundhedsdatastyrelsen) TDHCA. The health care authorities' classification system SKS (Sundhedsvæsenets Klassifikations System [SKS]).
25. Grove Krause T, Jakobsen S, Haarh M, Mølbak K. The Danish vaccination register. *Euro Surveill*. 2012;17:17.
26. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet*. 2021;397(10280):1204-1212. doi:10.1016/S0140-6736(21)00575-4
27. Solera JT, Árbol BG, Alshahrani A, et al. Impact of vaccination and early monoclonal antibody therapy on COVID-19 outcomes in organ transplant recipients during the omicron wave. *Clin Infect Dis*. 2022;75:2193-2200.
28. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399(10332):1303-1312. doi:10.1016/S0140-6736(22)00462-7
29. Zaqout A, Almaslamani MA, Chemaitelly H, et al. Effectiveness of the neutralizing antibody sotrovimab among high-risk patients with mild-to-moderate SARS-CoV-2 in Qatar. *Int J Infect Dis*. 2022;124:96-103. doi:10.1016/j.ijid.2022.09.023
30. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antiviral agents against the SARS-CoV-2 omicron subvariant BA.2. *N Engl J Med*. 2022;386(15):1475-1477. doi:10.1056/NEJMc2201933
31. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis*. 2022;22(5):622-635. doi:10.1016/S1473-3099(21)00751-9
32. Huang DT, McCreary EK, Bariola JR, et al. Effectiveness of Casirivimab-Imdevimab and Sotrovimab during a SARS-CoV-2 Delta variant surge: a cohort study and randomized comparative effectiveness trial. *JAMA Netw Open*. 2022;5(7):e2220957. doi:10.1001/jamanetworkopen.2022.20957
33. Dhand A, Okumura K, Wolfe K, et al. Sotrovimab for treatment of COVID-19 in solid organ transplant recipients. *Transplantation*. 2022;106(7):e336-e337. doi:10.1097/TP.0000000000004136
34. Pinchera B, Buonomo AR, Scotto R, et al. Sotrovimab in solid organ transplant patients with early, mild/moderate SARS-CoV-2 infection: a single-center experience. *Transplantation*. 2022;106(7):e343-e345. doi:10.1097/TP.0000000000004150
35. Yetmar ZA, Beam E, O'Horo JC, et al. Outcomes of bebtelovimab and sotrovimab treatment of solid organ transplant recipients with mild-to-moderate coronavirus disease 2019 during the omicron epoch. *Transpl Infect Dis*. 2022;24(4):e13901. doi:10.1111/tid.13901
36. Aggarwal NR, Beaty LE, Bennett TD, et al. Real world evidence of the neutralizing monoclonal antibody Sotrovimab for preventing hospitalization and mortality in COVID-19 outpatients. *J Infect Dis*. 2022;226:2129-2136.
37. Piccicacco N, Zeitler K, Ing A, et al. Real-world effectiveness of early remdesivir and sotrovimab in the highest-risk COVID-19 outpatients during the omicron surge. *J Antimicrob Chemother*. 2022;77(10):2693-2700. doi:10.1093/jac/dkac256
38. Aggarwal NR, Beaty LE, Bennett TD, et al. Change in effectiveness of Sotrovimab for preventing hospitalization and mortality for at-risk COVID-19 outpatients during an omicron BA.1 and BA.1.1-predominant phase. *Int J Infect Dis*. 2022;S1201-9712:00540-9. doi:10.1016/j.ijid.2022.10.002

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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