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Real-world Evidence of the Effects of Novel Treatments for COVID-19 on Mortality: A Nationwide Comparative Cohort Study of Hospitalized Patients in the First, Second, Third, and Fourth Waves in the Netherlands

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Background. Large clinical trials on drugs for hospitalized coronavirus disease 2019 (COVID-19) patients have shown significant effects on mortality. There may be a discrepancy with the observed real-world effect. We describe the clinical characteristics and outcomes of hospitalized COVID-19 patients in the Netherlands during 4 pandemic waves and analyze the association of the newly introduced treatments with mortality, intensive care unit (ICU) admission, and discharge alive.

Methods. We conducted a nationwide retrospective analysis of hospitalized COVID-19 patients between February 27, 2020, and December 31, 2021. Patients were categorized into waves and into treatment groups (hydroxychloroquine, remdesivir, neutralizing severe acute respiratory syndrome coronavirus 2 monoclonal antibodies, corticosteroids, and interleukin [IL]-6 antagonists). Four types of Cox regression analyses were used: unadjusted, adjusted, propensity matched, and propensity weighted.

Results. Among 5643 patients from 11 hospitals, we observed a changing epidemiology during 4 pandemic waves, with a decrease in median age (67–64 years; $P < .001$), in in-hospital mortality on the ward (21%–15%; $P < .001$), and a trend in the ICU (24%–16%; $P = .148$). In ward patients, hydroxychloroquine was associated with increased mortality (1.54; 95% CI, 1.22–1.96), and remdesivir was associated with a higher rate of discharge alive within 29 days (1.16; 95% CI, 1.03–1.31). Corticosteroids were associated with a decrease in mortality (0.82; 95% CI, 0.69–0.96); the results of IL-6 antagonists were inconclusive. In patients directly admitted to the ICU, hydroxychloroquine, corticosteroids, and IL-6 antagonists were not associated with decreased mortality.

Conclusions. Both remdesivir and corticosteroids were associated with better outcomes in ward patients with COVID-19. Continuous evaluation of real-world treatment effects is needed.

Keywords. COVID-19; SARS-CoV-2; antiviral; epidemiology; immunosuppressive treatments.

Since December 2019, coronavirus disease 2019 (COVID-19) has spread across the world, resulting in a global pandemic [1, 2]. The first case of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the Netherlands was confirmed on February 27, 2020. Two and a half years later, >8 million cases have been registered nationwide. As of January 2022, 4 waves of COVID-19 patients have been identified in the Netherlands (March 2020–June 2020, July 2020–January 2021, February 2021–June 2021, and July 2021–January 2022), which have resulted in >20 000 deaths [3]. The clinical characteristics and outcomes of hospitalized COVID-19 patients have changed during the pandemic waves. Compared with the first, the later waves were less deadly, they involved younger patients with fewer comorbidities, and the disease presentation was less severe [4, 5]. This improvement is, at least partly, due to extensive testing [6] and the development of vaccines against SARS-CoV-2, both extremely effective

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at preventing severe disease [7]. A small minority of fully vaccinated persons still develop severe COVID-19, but when comparing vaccinated hospitalized COVID-19 patients with unvaccinated patients, they are older, have more comorbidities, and have a higher rate of immunosuppression [8].

During the rapid increase of hospitalizations for COVID-19, novel drug treatments have been tested and, if initial results were encouraging, rapidly implemented in everyday clinical practice through evidence-based guidelines [9–12]. Landmark randomized controlled trials studied antiviral agents (remdesivir [13], molnupiravir [14]), SARS-CoV-2-neutralizing monoclonal antibodies (mAbs; casirivimab/imdevimab [15] and sotrovimab [16]), and immunosuppressive drugs (dexamethasone [17], recombinant interleukin [IL]-1 [18], the IL-6-receptor antagonists tocilizumab and sarilumab [19]) among hospitalized COVID-19 patients [9–11]. Treatments have also been discarded after initial guideline recommendations, such as the use of broad-spectrum antibiotics for all admitted patients [20], lopinavir/ritonavir [21], and hydroxychloroquine [22].

For hospitalized patients with suspected or confirmed COVID-19, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, the global Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP), the World Health Organization's (WHO's) Solidarity, and the National Institutes of Health (NIH)–initiated Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) platform trials have been instrumental in identifying treatments that have an impact on mortality [11]. More specifically, the RECOVERY investigators reported that treatment with dexamethasone resulted in an absolute reduction in 28-day mortality of 12.1% among patients receiving invasive mechanical ventilation (IMV) compared with usual care and of 2.9% among those receiving oxygen without IMV [17], treatment with anti-IL-6-receptor antagonists resulted in an absolute reduction in 28-day mortality of 4% [19], and for casirivimab and imdevimab this reduction was 6% in seronegative patients [15]. However, there seems to be a discrepancy between the expected beneficial impact of the implementation of these novel treatment modalities on mortality and the observed real-world effect [23].

Despite all the aforementioned COVID-19 treatments, mortality among patients hospitalized for moderate to severe COVID-19 remains high [24, 25]. Therefore, we aim to describe and compare the clinical characteristics and outcomes for hospitalized COVID-19 patients in the Netherlands during the 4 pandemic waves. Furthermore, we aim to analyze the association of the newly introduced treatments for COVID-19 with in-hospital mortality, 12-week mortality, intensive care unit (ICU) admission, and discharged alive within 29 days.

METHODS

Study Design, Population, and Data Collection

This study was conducted using data from 2 observational cohort studies, that is, the Dutch National Intensive Care Evaluation (NICE) registry [26] and the COVIDPredict [27]. Nationwide aggregated data on hospitalization and outcome of all COVID-19 patients consecutively admitted to all hospitals in the Netherlands were extracted from the NICE registry. The COVIDPredict study is a retrospective observational cohort study including all patients with confirmed COVID-19 from 11 Dutch hospitals varying from peripheral hospitals to large teaching and academic medical centers across the Netherlands. Included patients were aged ≥18 years and hospitalized between February 27, 2020, and December 31, 2021, with confirmed COVID-19, defined as a positive SARS-CoV-2 polymerase chain reaction or a CORADS computed tomography (CT) thorax score >4 at admission [28]. All readmissions for COVID-19 within this time frame were also included. More details regarding patient selection and data collection can be found in the Supplementary Methods.

Patient Consent

The medical ethics committee of the Amsterdam University Medical Centers (Amsterdam UMC; 20.131) stated that no medical ethics approval was required for the NICE registry and approved the design of this work and an opt-out procedure (and waived the need for informed consent) for the COVIDPredict.

Outcomes

The primary outcome was in-hospital mortality. The secondary outcomes were 12-week mortality, ICU admission, and discharge alive within 29 days. Patients were categorized into waves based on date of hospitalization to describe the changing epidemiology during the pandemic in the Netherlands. The definition of the waves can be found in the Supplementary Methods. To analyze the treatment effects, patients were categorized into the following treatment groups: hydroxychloroquine, remdesivir, neutralizing SARS-CoV-2 mAbs, corticosteroids, and IL-6 antagonists. Patients were analyzed comparing patients who received the treatment of interest vs all those who did not. Because of the observational nature of our data, overlap of treatments was allowed. Further specification on the medications used can be found in the Supplementary Methods.

Statistical Analysis

Data distribution was analyzed using Shapiro-Wilk tests and histogram plots. Baseline characteristics, treatments, and outcomes of patients admitted per wave were compared using a 1-way analysis of variance for parametric data, a

Kruskal-Wallis test for nonparametric data, and a chi-square test for categorical data, all unadjusted.

Patients admitted directly to the ward and patients admitted directly to the ICU were analyzed separately. Directly admitted to the ward was defined as admitted to the ward directly from the emergency room; directly admitted to the ICU was defined as admitted to the ICU on the day of admission. For the rate of discharge alive analysis, data for patients who died after 29 days were censored at day 29, as previously performed in a large randomized clinical trial executing similar analyses [29]. Patients who were transferred before 29 days were censored. Given the time-dependent nature of treatment exposure, a landmark analysis was used; patients who survived to the landmark time point of 2 days after admission were included. More details regarding this landmark analysis and imputation of missing data can be found in the Supplementary Methods. To analyze in-hospital mortality, 12-week mortality, ICU admission, and discharge alive within 29 days, 4 different Cox regression analyses were used: (1) unadjusted, (2) adjusted for confounding variables, (3) using propensity matching, and (4) using inverse probability weighting. The variables used as confounders in the adjusted Cox regression, the inverse probability weighting, and the propensity score–matching analyses and the methods used for the propensity score matching and inverse probability weighting can be found in the Supplementary Methods. A P value of <.05 was considered statistically significant.

RESULTS

Nationwide aggregated data from the NICE registry showed that between February 27, 2020, and December 31, 2021, 89 110 patients with confirmed COVID-19 were admitted to the ward, and 16 590 patients, either directly or after deterioration, were admitted to the ICU in the Netherlands. Of these, 10 317 COVID-19 patients died on the ward and 4511 in the ICU. In this time period, 6 novel drug treatment modalities were implemented through national guidelines [10], either as standard or optional care for patients hospitalized for COVID-19: lopinavir/ritonavir, hydroxychloroquine, remdesivir, casirivimab/imdevimab or sotrovimab, dexamethasone, and tocilizumab or sarilumab (Figure 1*A*).

Of the 8093 patients included in the COVIDPredict database, 5643 (69.7%) met our inclusion criteria; 5187 patients were directly admitted to the ward, and 456 patients were directly admitted to the ICU (see the Supplementary Results for more detailed information regarding the excluded patients). The overall median age of patients admitted to the ward for COVID-19 across all waves (interquartile range [IQR]) was 66 (56–77) years, and 3048 (59%) were males. Thirteen percent (n = 686) of the patients were admitted to the ICU, and 17% (n = 891) died during hospitalization (Table 1). For those patients directly admitted to the ICU across all waves, the median age (IQR) was 65 (57–72) years, and 340 (75%) were males. Twenty-six percent (n = 119) of patients died in the ICU, and 33% (n = 152) died during admission (Tables 1 and 2).

Changing Epidemiology—Ward

The percentage of males decreased over the waves (from 61%, n = 1499, in wave 1 to 51%, n = 247, in wave 4; $P < .001$), as well as the median age (from 68 to 65 years; $P < .001$) (Table 1). The median Modified Early Warning Score (MEWS) on admission (IQR) was lower in wave 3 compared with the first wave (2 [1–3] compared with 3 [1–4]; $P = .002$). The crude in-hospital mortality of ward patients decreased from 21% (n = 510) in wave 1 to 15% (n = 74) in wave 4 ($P < .001$), while the crude ICU mortality in patients first admitted to the ward showed a positive trend (29%, n = 88, in wave 1 to 16%, n = 14, in wave 4; $P = .057$) (Table 1). Data regarding bloodstream infections (BSIs) can be found in the Supplementary Results and Supplementary Table 1.

With regards to the antiviral and immunosuppressive drugs administered, lopinavir/ritonavir and hydroxychloroquine were almost solely administered in wave 1 and remdesivir mostly in wave 2. Corticosteroids became standard treatment for hospitalized patients needing oxygen in wave 2, IL-6 antagonists in wave 3, and neutralizing SARS-CoV-2 mAbs were solely given in wave 4 (Figure 1*B;* Supplementary Figure 1). Overlap in treatments is specified in Supplementary Table 2. The most frequently occurring combinations were corticosteroids with remdesivir, IL-6 antagonists, or neutralizing SARS-CoV-2 mAbs.

Changing Epidemiology—ICU

For those patients admitted to the ICU, the median age decreased over time (from 66 years in wave 1 to 62 years in wave 4; $P = .026$) (Table 2). The crude ICU mortality showed a positive trend during the 4 waves (from 30%, n = 60, in wave 1 to 16%, n = 8, in wave 4; $P = .148$). More data on the changing epidemiology can be found in Figure 2*B*, Table 2, the Supplementary Results, and Supplementary Tables 3 and 4.

Association of Antivirals With Mortality—Ward

Over 80% of antiviral and/or immunosuppressive treatments were initiated within the first 2 days after hospital or ICU admission (Supplementary Figure 2). Therefore, landmarking at 2 days seemed the optimal time window for the analyses. Percentages of missing variables, information on propensity score matching and weighting, and the violation of the proportionality assumption can be found in the Supplementary Results, Supplementary Figures 3, 4, and 5, and Supplementary Table 5.

Ward patients treated with hydroxychloroquine in the first 2 days after admission showed an increased risk of mortality, with a hazard ratio (HR) of 1.65 (95% CI, 1.29–2.12) for

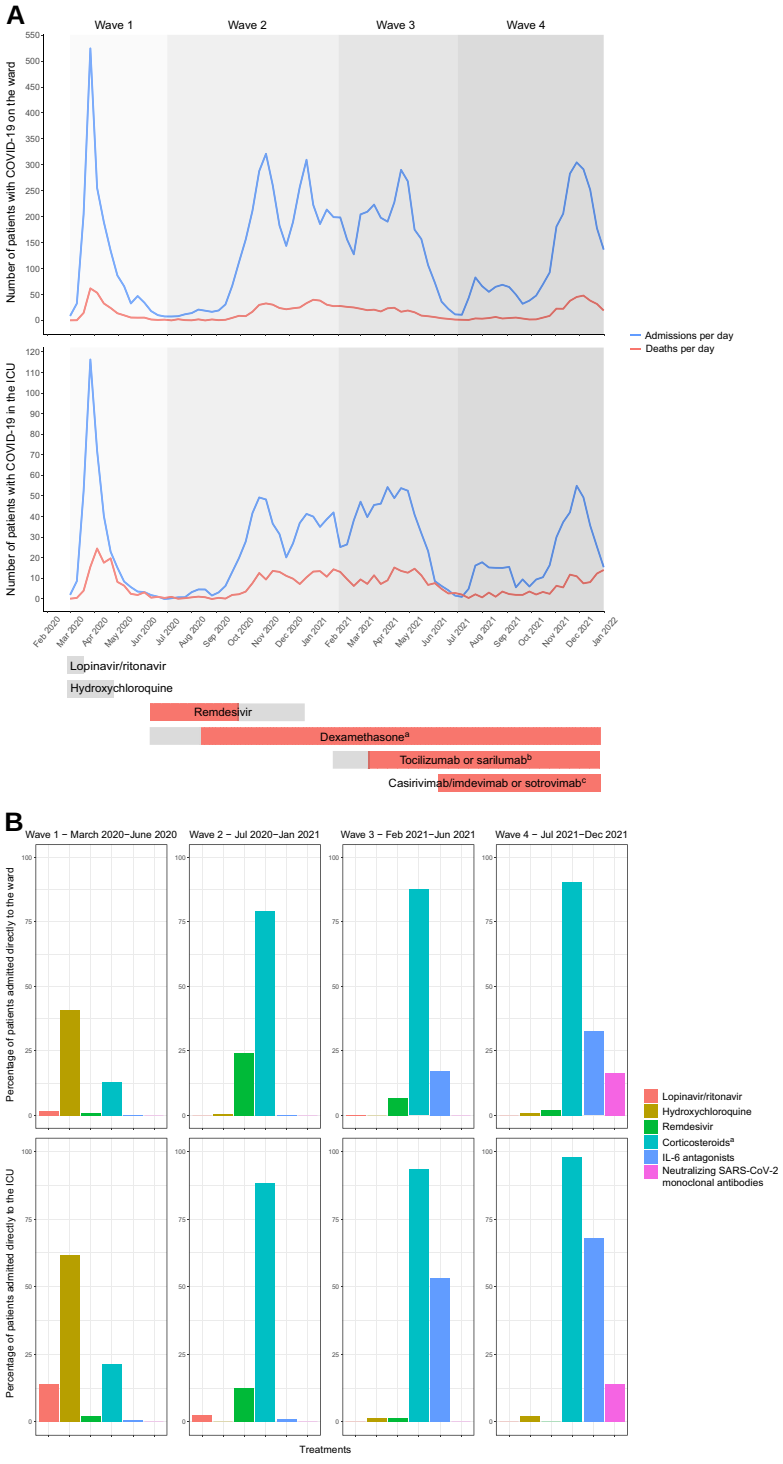

Figure 1. Admissions, mortality, and treatments for COVID-19 in the first, second, third, and fourth waves in the Netherlands. A, Admissions, mortality, and novel antiviral and immunosuppressive treatments for COVID-19 in the first, second, third, and fourth waves in the Netherlands. Between February 27, 2020, and December 31, 2021, 89 110 patients with confirmed COVID-19 were admitted to the ward and 16 590 patients to the ICU in the Netherlands; 10 317 COVID-19 patients died on the ward and 4511 in the ICU. In this time period, 6 novel drug treatment modalities were implemented through national guidelines [10], either as standard or optional care for patients hospitalized because of COVID-19. Gray bars: included in national treatment guidelines as optional care; red bars: included as standard care. [a]Dexamethasone was first only recommended for ICU patients, since September 29, 2020, also for ward patients. [b]IL-6 antagonists were first only recommended for ICU patients, since March 9, 2021, also for ward patients. [c]Casirivimab/imdevimab was recommended until December 23, 2021; sotrovimab was recommended since December 23, 2021. B, Administration of novel antiviral and immunosuppressive treatments for hospitalized COVID-19 in the first, second, third, and fourth waves in the Netherlands. The percentage of patients included in the COVIDPredict trial treated with the 6 novel drug treatment modalities implemented through national guidelines in the time period between February 27, 2020, and December 31, 2021. [a]Included dexamethasone, prednisolone, hydrocortisone, and methylprednisolone. Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Characteristics and Outcomes of Patients Directly Admitted to the Ward

…	All Patients	1st Wave	2nd Wave	3rd Wave	4th Wave	*P*
Number of patients admitted with COVID-19	5187	2458	1542	701	486	
Dominant strain	…	Original (Wuhan) strain	Original (Wuhan) strain	Alpha	Delta	
Demographics	…	…	…	…	…	
Sex—male, No. (%)	3048 (58.8)	1499 (61.0)	898 (58.2)	404 (57.7)	247 (50.9)[a,b]	<.001
Age, median [IQR], y	66.10 [56.00–77.00]	68.00 [57.00–78.00]	67.00 [57.00–77.00]	63.00 [52.00–72.00][a,b]	65.00 [51.00–77.00][a,b]	<.001
Body mass index, median [IQR], kg/m^2	27.47 [24.52–31.41]	27.16 [24.39–30.83]	27.51 [24.58–31.53]	28.06 [24.85–32.44][a]	28.08 [24.66–32.72][a]	.001
Race, No. (%)	…	…	[a]	[a]	[a,c]	<.001
Arab	417 (9.7)	171 (8.1)	144 (11.3)	56 (10.9)	46 (11.4)	
Asian	227 (5.3)	98 (4.6)	81 (6.4)	37 (7.2)	11 (2.7)	
Black	428 (10.0)	144 (6.8)	155 (12.2)	70 (13.7)	59 (14.7)	
White	3087 (71.8)	1651 (78.2)	840 (66.0)	321 (62.7)	275 (68.4)	
Other	139 (3.2)	47 (2.2)	53 (4.2)	28 (5.5)	11 (2.7)	
Baseline characteristics	…	…	…	…	…	
Days since onset of symptoms, median [IQR]	8.00 [5.00–11.00]	7.00 [5.00–12.00]	8.00 [5.00–11.00]	9.00 [6.00–11.00][a,b]	7.00 [4.00–9.00][a,b,c]	<.001
Transfer from other hospital, No. (%)	281 (5.4)	49 (2.0)	93 (6.0)[a]	109 (15.5)[a,b]	30 (6.2)[a,c]	<.001
Do not resuscitate and/or intubate order, No. (%)	1426 (31.0)	722 (35.8)	423 (28.9)[a]	147 (21.7)[a,b]	134 (30.0)[c]	<.001
Vaccinated against SARS-CoV-2, No. (%)	261 (9.2)	0 (0.0)	1 (0.1)	56 (8.8)[a,b]	204 (45.0)[a,b,c]	<.001
Medical history	…	…	…	…	…	
Patients with comorbidities,[d] No. (%)	3843 (83.7)	1778 (83.2)	1188 (85.4)	493 (81.8)	384 (83.7)	.170
Number of comorbidities,[d] median [IQR]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	2.00 [1.00–3.00][a,b]	2.00 [1.00–3.00]	.002
Asthma or other chronic pulmonary disease, No. (%)	1307 (25.4)	632 (26.0)	419 (27.3)	160 (22.9)	96 (19.8)[a,b]	.003
Chronic cardiac disease, No. (%)	1537 (29.9)	750 (30.8)	455 (29.8)	180 (25.9)	152 (31.3)	.081
Chronic kidney disease, No. (%)	672 (13.1)	299 (12.3)	214 (14.0)	90 (12.9)	69 (14.2)	.406
Diabetes, No. (%)	1058 (20.4)	464 (18.9)	360 (23.3)[a]	138 (19.7)	96 (19.8)	.007
Hypertension, No. (%)	2300 (44.7)	1127 (46.1)	701 (46.0)	274 (39.3)[a,b]	198 (41.0)	.003
Malignancy, No. (%)	385 (7.5)	196 (8.1)	118 (7.7)	39 (5.6)	32 (6.6)	.140
Organ transplantation, No. (%)	128 (2.5)	32 (1.3)	30 (2.0)	36 (5.2)[a,b]	30 (6.4)[a,b]	<.001
Disease severity	…	…	…	…	…	
MEWS, median [IQR]	2.00 [1.00–4.00]	3.00 [1.00–4.00]	2.00 [1.00–4.00]	2.00 [1.00–3.00][a]	3.00 [2.00–4.00][c]	<.001
CT Severity Score, median [IQR]	10.00 [6.00–14.00]	8.00 [5.00–12.00]	11.00 [8.00–15.00][a]	12.00 [10.00–16.00][a,b]	12.00 [9.00–15.00][a]	<.001
4C Mortality Score, median [IQR]	10.00 [7.00–13.00]	10.00 [6.00–13.00]	10.00 [7.00–13.00]	9.00 [6.00–12.00][b]	10.00 [7.00–13.00][c]	.002
Outcomes	…	…	…	…	…	
Venous thromboembolism, No. (%)	278 (5.4)	133 (5.4)	75 (4.9)	43 (6.1)	27 (5.6)	.654
Length of hospital stay, median [IQR], d	6.00 [3.00–11.00]	5.00 [3.00–10.00]	6.00 [3.00–10.00][a]	7.00 [4.00–12.00][a,b]	8.00 [4.00–14.00][a,b]	<.001
In-hospital mortality, No. (%)	891 (17.2)	510 (20.7)	223 (14.5)[a]	84 (12.0)[a]	74 (15.2)[a]	<.001
12-wk mortality, No. (%)	973 (18.8)	550 (22.4)	249 (16.1)[a]	96 (13.7)[a]	78 (16.0)[a]	<.001
ICU admission, No. (%)	686 (13.2)	309 (12.6)	172 (11.2)	119 (17.0)[a,b]	86 (17.7)[a,b]	<.001
Mechanical ventilation, No. (%)	497 (72.9)	263 (85.7)	112 (65.5)[a]	74 (62.7)[a]	48 (55.8)[a]	<.001
Ventilator-free days, median [IQR]	13.00 [0.00–22.00]	8.00 [0.00–19.00]	13.00 [0.00–23.00]	20.00 [0.00–25.00][a]	19.50 [0.00–23.00][a]	<.001
Length of ICU stay, median [IQR], d	8.00 [3.00–16.00]	10.00 [5.00–19.00]	7.00 [2.00–15.00][a]	7.00 [3.00–13.00][a]	5.00 [2.00–11.00][a]	<.001
ICU mortality, No. (%)	167 (24.3)	88 (28.5)	42 (24.4)	23 (19.3)	14 (16.3)	.057

Abbreviations: CT, computed tomography; ICU, intensive care unit; MEWS, Modified Early Warning Score.

[a]Significant vs first wave using a Dunn's test of multiple comparisons using rank sums for nonparametric continuous variables, a Tukey test for parametric continuous variables, and a Bonferroni correction for categorical variables.

[b]Significant vs second wave using a Dunn's test of multiple comparisons using rank sums for nonparametric continuous variables, a Tukey test for parametric continuous variables, and a Bonferroni correction for categorical variables.

[c]Significant vs third wave using a Dunn's test of multiple comparisons using rank sums for nonparametric continuous variables, a Tukey test for parametric continuous variables, and a Bonferroni correction for categorical variables.

[d]Comorbidities include chronic cardiac disease, hypertension, chronic pulmonary disease, asthma, chronic kidney disease, liver disease, chronic neurologic disease, malignancy, chronic hematologic disease, HIV or AIDS, diabetes, rheumatic disorder, auto-immune disease, dementia, and obesity.

in-hospital mortality and an HR of 1.52 (95% CI, 1.19–1.94) for 12-week mortality, and were at decreased risk for discharge alive, with an HR of 0.78 (95% CI, 0.68–0.91) in the propensity score–matched cohort. Propensity score weighting analysis showed similar results (Figure 2A; Supplementary Tables 6 and 7).

For remdesivir, the opposite association was seen. Patients treated with remdesivir showed decreased in-hospital mortality (9% vs 15%; $P = .015$) and increased rates of discharge alive (89% vs 82%; $P = .011$) using propensity score weighting; however, this was not the case in the propensity score–matched cohort (Supplementary Table 6). Patients treated with remdesivir were more likely to be discharged alive, with an HR of 1.16 (95% CI, 1.03–1.31) in the propensity score–matched cohort and 1.23 (95% CI, 1.07–1.40) in the propensity score–weighted cohort (Figures 2A and 3A; Supplementary Table 7).

In patients treated with neutralizing SARS-CoV-2 mAbs, no significant association with mortality or being discharged alive was seen after adjusting for confounders. SARS-CoV-2 mAbs had a positive association with ICU admission in the propensity score–weighted cohort (2% vs 7%; $P = .041$) (Supplementary Table 6).

Association of Immunosuppressive Treatment With Mortality—Ward

Treatment with corticosteroids was significantly associated with lower in-hospital mortality and 12-week mortality and higher rates of discharge alive in the propensity score analyses (in-hospital mortality 12% vs 16%; $P = .003$; 12-week mortality 14% vs 17%; $P = .004$; and discharge alive within 29 days 85% vs 81%; $P = .002$). However, in the propensity score–weighted cohort, there was no significant difference (Figures 2*A* and 3*B* and *C*; Supplementary Table 6). Patients had a lower risk of in-hospital mortality (HR, 0.81; 95% CI, 0.69–0.96) and 12-week mortality (HR, 0.84; 95% CI, 0.71–0.98) in the propensity score–matched cohort (Figure 2*A*; Supplementary Table 7).

Patients treated with IL-6 antagonists showed increased 12-week mortality, ICU admission, and a lower number discharged alive in both the propensity score–matched cohort and the propensity score–weighted cohort (12-week mortality 26% vs 16%; $P = .007$; ICU admission 20% vs 6%; $P < .001$; and discharge alive within 29 days 72% vs 83% in the propensity score–weighted cohort; $P = .005$) (Figure 3D; Supplementary Table 6). Patients treated with IL-6 antagonists were at increased risk of ICU admission (HR, 1.98; 95% CI, 1.29–3.04; in the propensity score–matched cohort; HR, 2.13; 95% CI, 1.38–3.30; in the propensity score–weighted cohort) (Figure 2*A* and 3*E*; Supplementary Table 7).

Association of Antivirals and Immunosuppressive Treatment With Mortality—ICU

In patients directly admitted to the ICU who were treated with either hydroxychloroquine, corticosteroids, or IL-6 antagonists, no associations were seen with mortality or the rate of being discharged alive and use of any of these compounds. More data on the association of antivirals and immunosuppressive treatment with mortality can be found in Figure 3*F* and *G*, the Supplementary Results, and Supplementary Tables 8 and 9.

Since hydroxychloroquine is associated with a significant increase in mortality in patients directly admitted to the ward, we conducted a subanalysis excluding patients admitted in the first wave, as hydroxychloroquine was mostly administered in the first wave. In contrast to our main analyses, in patients admitted directly to the ICU in the second, third, and fourth waves, treatment with corticosteroids was associated with a significant decrease in in-hospital and 12-week mortality in the adjusted Cox regression (HR, 0.27; 95% CI, 0.09–0.75; HR, 0.33; 95% CI 0.11–0.89), this association was not seen in the propensity score–matched and propensity score–weighted analyses. See the Supplementary Results and Supplementary Figures 6 and 7 for more results.

DISCUSSION

In this observational cohort study of 5643 hospitalized COVID-19 patients, we observed a changing epidemiology during the 4 pandemic waves in the Netherlands. Over time, the percentage of males and the mean age of admitted patients decreased. While the in-hospital mortality of ward patients decreased over time, the in-hospital mortality of ICU patients did not change significantly. Using multiple Cox regression techniques, we found the following effects of the newly introduced COVID-19 drug treatments. First, hydroxychloroquine was associated with higher mortality and a lower rate of discharge alive. Second, remdesivir was positively associated in ward patients with the rate of being discharged alive within 29 days in all analyses. Third, in hospital SARS-CoV-2 monoclonal antibody treatment was associated with a lower rate of ICU admission but not mortality in the propensity score–weighted cohort of ward patients. Fourth, corticosteroid treatment was associated with mortality, and with higher rates of being discharged in the propensity score–matched cohort of patients directly admitted to the ward. Fifth, anti-IL-6 treatment in patients directly admitted to the ward was associated with increased mortality and ICU admission. Last, in patients directly admitted to the ICU who were treated with either hydroxychloroquine, corticosteroids, or IL-6 antagonists, no associations were seen with mortality or the rate of being discharged alive. As we investigated the real-life effectiveness of COVID-19 treatments, patients included in these analyses were often treated with >1 of the analyzed treatments.

Our findings on the changes in the patient characteristics of admitted patients and their outcomes during the consecutive waves of the pandemic are in line with several cohort studies

Table 2. Characteristics and Outcomes of Patients Admitted Directly to the ICU

…	All Patients	1st Wave	2nd Wave	3rd Wave	4th Wave	*P*
Number of patients admitted with COVID-19	456	201	128	77	50	
Dominant strain	…	Original (Wuhan) strain	Original (Wuhan) strain	Alpha	Delta	
Demographic characteristics	…	…	…	…	…	
Sex—male, No. (%)	340 (74.6)	157 (78.1)	93 (72.7)	53 (68.8)	37 (74.0)	.404
Age, median [IQR], y	65.00 [56.77–72.00]	66.10 [59.00–73.00]	64.50 [56.00–72.00]	64.00 [52.00–72.00]	62.00 [56.00–69.00]	.026
Body mass index, median [IQR], kg/m^2	28.04 [24.97–31.24]	27.76 [25.17–29.93]	27.26 [24.53–32.31]	28.74 [25.56–33.33]	29.06 [24.81–32.14]	.318
Race, No. (%)	…	…	…	…	…	.207
Arab	40 (11.7)	16 (10.0)	13 (14.4)	8 (15.7)	3 (7.1)	
Asian	27 (7.9)	9 (5.6)	7 (7.8)	6 (11.8)	5 (11.9)	
Black	27 (7.9)	10 (6.2)	9 (10.0)	2 (3.9)	6 (14.3)	
White	233 (67.9)	119 (74.4)	55 (61.1)	31 (60.8)	28 (66.7)	
Other	16 (4.7)	6 (3.8)	6 (6.7)	4 (7.8)	0 (0.0)	
Baseline characteristics	…	…	…	…	…	
Days since onset of symptoms, median [IQR]	8.00 [6.00–11.25]	9.00 [7.00–13.00]	8.00 [6.00–10.00]	9.00 [6.00–12.00]	8.50 [5.00–11.00]	.181
Transfer from other hospital, No. (%)	109 (23.9)	43 (21.4)	32 (25.0)	28 (36.4)	6 (12.0)[c]	.010
Do not resuscitate and/or intubate order, No. (%)	76 (18.2)	35 (19.9)	18 (15.0)	14 (18.4)	9 (19.6)	.748
Vaccinated against SARS-CoV-2, No. (%)	25 (9.2)	0 (0.0)	0 (0.0)	7 (11.1)[b]	18 (36.7)[a,b,c]	<.001
Medical history	…	…	…	…	…	
Patients with comorbidities,[d] No. (%)	336 (80.6)	147 (82.6)	97 (80.2)	55 (79.7)	37 (75.5)	.727
Number of comorbidities,[d] median [IQR]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	2.00 [1.00–3.00]	.921
Asthma or other chronic pulmonary disease, No. (%)	110 (24.4)	55 (27.8)	27 (21.1)	19 (25.7)	9 (18.0)	.368
Chronic cardiac disease, No. (%)	117 (26.1)	63 (32.0)	23 (18.1)[a]	20 (27.0)	11 (22.0)	.042
Chronic kidney disease, No. (%)	44 (9.8)	20 (10.2)	12 (9.4)	7 (9.3)	5 (10.0)	.994
Diabetes, No. (%)	112 (24.6)	50 (24.9)	41 (32.0)	14 (18.2)	7 (14.0)	.036
Hypertension, No. (%)	208 (46.1)	101 (51.0)	55 (43.0)	30 (40.0)	22 (44.0)	.303
Malignancy, No. (%)	21 (4.7)	10 (5.2)	7 (5.6)	3 (4.0)	1 (2.0)	.756
Organ transplantation, No. (%)	5 (1.1)	2 (1.0)	2 (1.6)	1 (1.3)	0 (.0)	.844
Disease severity	…	…	…	…	…	
MEWS, median [IQR]	4.00 [3.00–6.00]	4.00 [3.00–6.00]	4.00 [3.00–5.00]	4.00 [3.00–6.00]	4.00 [2.00–6.00]	.582
CT Severity Score, median [IQR]	18.00 [14.75–22.00]	17.00 [5.00–21.00]	18.00 [15.00–21.00]	20.00 [18.00–22.00]	18.00 [15.00–23.00]	.078
4C Mortality Score, median [IQR]	12.00 [10.00–14.00]	12.00 [10.00–14.00]	12.00 [9.00–14.00]	11.00 [9.00–14.00]	11.00 [10.00–13.00]	.218
Clinical course data	…	…	…	…	…	
Venous thromboembolism, No. (%)	80 (17.5)	41 (20.4)	22 (17.2)	9 (11.7)	8 (16.0)	.384
Mechanical ventilation, No. (%)	346 (76.4)	168 (84.4)	92 (72.4)	54 (70.1)[a]	32 (64.0)[a]	.003
Ventilator-free days, median [IQR], d	11.09 (10.61)	9.18 (9.82)	11.26 (11.22)	15.20 (10.69)[a]	13.45 (10.53)	.002
Length of hospital stay, median [IQR], d	15.00 [9.00–26.25]	17.00 [9.00–31.00]	14.00 [10.00–22.00]	13.50 [9.00–23.00]	21.00 [8.00–26.00]	.694
Length of ICU stay, median [IQR], d	9.00 [4.00–18.50]	11.00 [5.00–23.00]	8.00 [3.00–14.00]	7.00 [3.00–13.00][a]	7.00 [3.00–13.00]	.004
ICU mortality, No. (%)	119 (26.1)	60 (29.9)	35 (27.3)	16 (20.8)	8 (16.0)	.148
In-hospital mortality, No. (%)	152 (33.3)	79 (39.3)	39 (30.5)	18 (23.4)	16 (32.0)	.067
12-wk mortality, No. (%)	156 (34.2)	80 (39.8)	41 (32.0)	18 (23.4)	17 (34.0)	.069

Abbreviations: CT, computed tomography; ICU, intensive care unit; MEWS, Modified Early Warning Score.

[a]Significant vs first wave using a Dunn's test of multiple comparisons using rank sums for nonparametric continuous variables, a Tukey test for parametric continuous variables, and a Bonferroni correction for categorical variables.

[b]Significant vs second wave using a Dunn's test of multiple comparisons using rank sums for nonparametric continuous variables, a Tukey test for parametric continuous variables, and a Bonferroni correction for categorical variables.

[c]Significant vs third wave using a Dunn's test of multiple comparisons using rank sums for nonparametric continuous variables, a Tukey test for parametric continuous variables, and a Bonferroni correction for categorical variables.

[d]Comorbidities include chronic cardiac disease, hypertension, chronic pulmonary disease, asthma, chronic kidney disease, liver disease, chronic neurologic disease, malignancy, chronic hematologic disease, HIV or AIDS, diabetes, rheumatic disorder, auto-immune disease, dementia, and obesity.

performed in Italy, Spain, and the United States in which the second [4, 30, 31] and third waves [32, 33] were compared with the first. We now further expand this body of literature by including a fourth wave. We observed a nonsignificant decrease in ICU mortality during the 4 pandemic waves, possibly related to the sample size of our ICU cohort. In previously published data from the NICE including all COVID-19 patients admitted to the ICU in the Netherlands, a decreased mortality rate in the third wave compared with the first and second was indeed found [31]. Of interest, a recent study from South Africa found a different pattern of characteristics and outcomes in patients hospitalized with COVID-19 in the early phase of the fourth wave compared with earlier waves, with younger patients having fewer comorbidities, and a decrease in severity and mortality [5].

The increased mortality associated with hydroxychloroquine use is in line with earlier meta-analyses [22]. The same holds true for the effectiveness of remdesivir in nonventilated patients with COVID-19 requiring oxygen therapy [29, 34]. This is of interest, as the use of remdesivir was no longer advised in Dutch national guidelines after the negative interim analysis of the SOLIDARITY trial on remdesivir in admitted COVID-19 patients, published late 2020 [10, 35]. In contrast to earlier reports on the beneficial use of SARS-CoV-2 mAbs in (seronegative) hospitalized COVID-19 patients, we did not observe an association with mortality, although the sample size in this subanalysis was relatively low [11, 15].

The most recent Cochrane review assessing the treatment effect of systemic corticosteroids concluded that this treatment leads to slightly reduced all-cause mortality in people hospitalized for symptomatic COVID-19 with a risk ratio of 0.89 (95% CI, 0.80–1.00) [36], similar to our results in patients directly admitted to the ward. In our ICU cohort, anti-IL-6 treatment was not associated with decreased mortality. This is in accordance with a Bayesian reanalysis of a previous meta-analysis of 15 studies of hospitalized patients with COVID-19 treated with tocilizumab and corticosteroids, in which the use of oxygen only and noninvasive ventilation (NIV) was associated with a probability of a clinically meaningful mortality benefit from tocilizumab [37]. This study reported no convincing evidence for patients receiving IMV to benefit from tocilizumab [37].

The strengths of the present study are worth emphasizing. To our knowledge, this is the first time that the real-world effectiveness of the novel introduced treatments for COVID-19 have been studied this extensively. Another strength is the use of a landmark analysis in order to prevent bias; many cohort studies investigating treatment effect introduce biases, mainly selection and immortal time bias, leading to nonmeaningful results [23]. Lastly, as treatment for COVID-19 might be dependent on baseline characteristics linked to adverse outcomes like mortality, ICU admission, and a longer hospital stay, we used multiple Cox regression techniques to deal with this confounding and produce robust results. The outcome of ICU admission was most likely not influenced by a shortage of ICU beds. In the Netherlands, a critical shortage of ICU beds was a continuous threat, especially during the first wave [38], but did not reach the critical threshold upon which the national Intensive Care Triage Protocol had to be implemented. This study has several limitations. First, the changes in variants of the SARS-CoV-2 virus during our study period; even though we corrected for several baseline characteristics, the new genetic mutations could have had an influence on the outcomes and treatment effects. Second, the vaccination status of patients was only systematically collected after the SARS-CoV-2 vaccinations started to become widely available; therefore, we did not incorporate it into our analyses. Vaccines against SARS-CoV-2, all extremely effective at preventing severe disease and lowering mortality [7], have probably influenced the treatment effect. Unfortunately, this information was missing in our data. Third, even though several types of analyses were used, we were not able to match patients directly admitted to the ward treated with IL-6 antagonists with those not treated on admission, leading to a higher ICU admission rate in patients treated with IL-6 antagonists. Fourth, in patients directly admitted to the ward treated with neutralizing SARS-CoV-2 mAbs, the event rate was low, with only 1 deceased patient and 3 admitted to the ICU. Fifth, not all adjusted Cox regression analyses met the proportionality assumption. However, all analyses using propensity scores met this assumption; these are overall more favorable analyses than traditional regression analyses [39]. Several treatment changes over the pandemic waves were not analyzed here as our focus was on antiviral and immunosuppressive agents. In some hospitals in the Netherlands, higher prophylactic or therapeutic-dose low–molecular weight heparin was given in the ICU after a positive influence on mortality was published [40]. Furthermore, NIV and high-flow nasal oxygen therapy were more often used during later waves compared with IMV [31], reflected by more ICU admissions with lower intubation rates during the waves in our data.

Several clinicians and researchers have advocated for a more personalized approach in the treatment of COVID-19 patients [41]. The host response to SARS-CoV-2 is complex, with pathways that can be both beneficial and destructive. Immunomodulatory agents modifying these pathways can be effective for some patients, while for others they can ineffective or even harmful [11]. For example, the use of corticosteroids showed significant survival benefits in patients with the hyperinflammatory phenotype [42], and in ICU-admitted patients a beneficial effect of corticosteroids was seen in older and more severely ill patients while mortality was increased when administered within 7 days of onset [43]. Early administration of tocilizumab was associated with improvement in oxygenation in patients with high IL-6, while patients with low IL-6 treated with tocilizumab showed similar mortality rates as patients

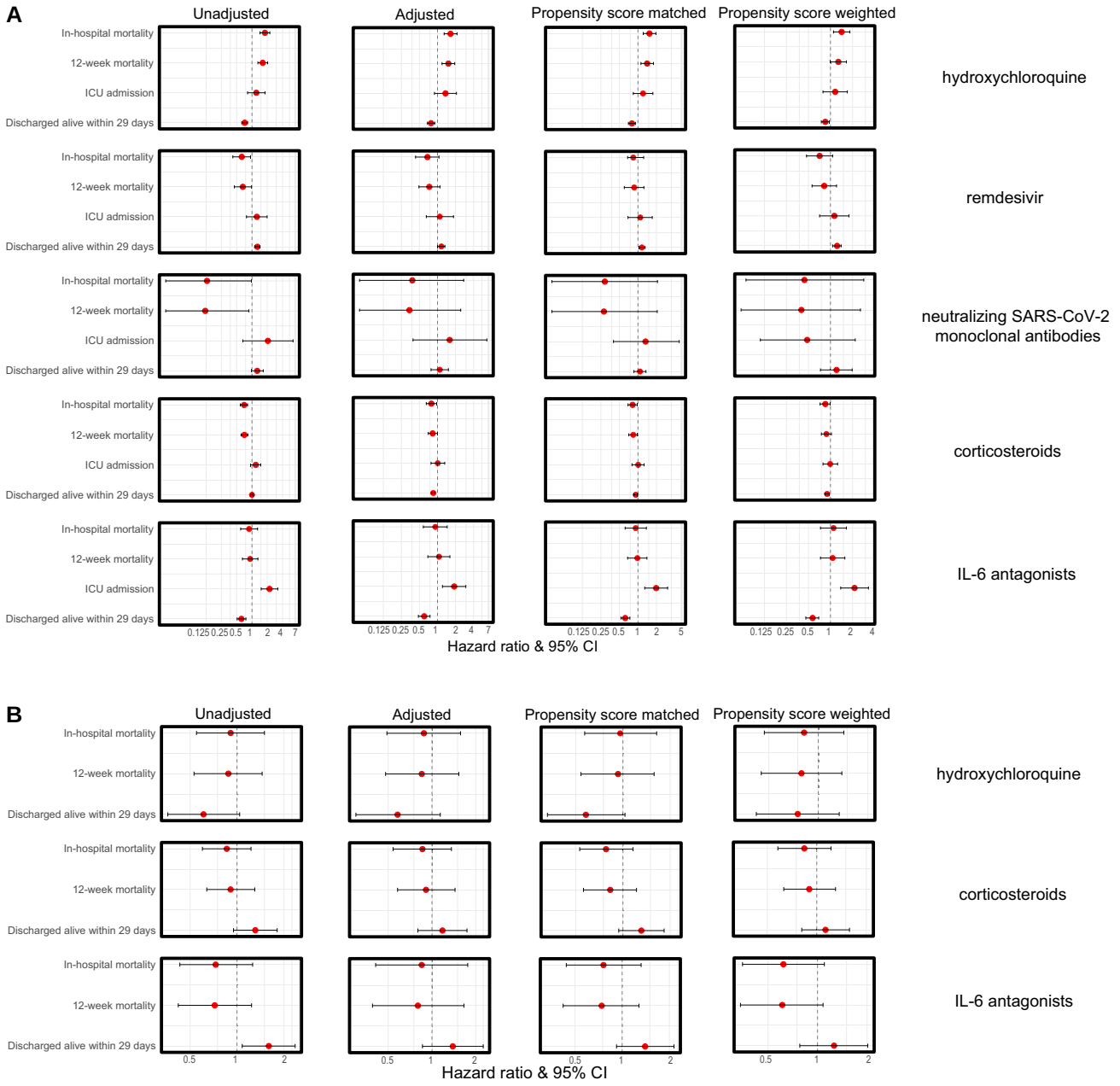

Figure 2. Hazard ratios of treatment effects per treatment group. A, Patients admitted directly to the ward. B, Patients admitted directly to the ICU. Remdesivir and SARS-CoV-2-neutralizing monoclonal antibodies were not analyzed given the small sample size. Abbreviations: ICU, intensive care unit; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

with high IL-6 not treated with tocilizumab [44]. In addition, targeted treatment with anakinra, an IL-1 receptor antagonist, reduced mortality in hospitalized patients at risk for unfavorable outcomes using baseline soluble urokinase plasminogen activator receptor (suPAR) as a biomarker [18]. This might be the future for more positive treatment effects in hospitalized COVID-19 patients. The variable treatment effects, depending on a patient's host response and disease severity, might explain some of the contrasts from clinical studies. Personalized immunotherapy in COVID-19 needs to be further investigated through randomized clinical trials by looking into the most favorable biomarker-driven therapies [11]. Finally, we know from milder viral pneumonia such as influenza that steroids result in worse outcomes [45]. It can be questioned whether steroids are still beneficial in the milder COVID-19 variants as the clinical phenotype becomes more and more an influenza-like virus.

In summary, we observed a changing epidemiology during the 4 pandemic COVID-19 waves in the Netherlands, with

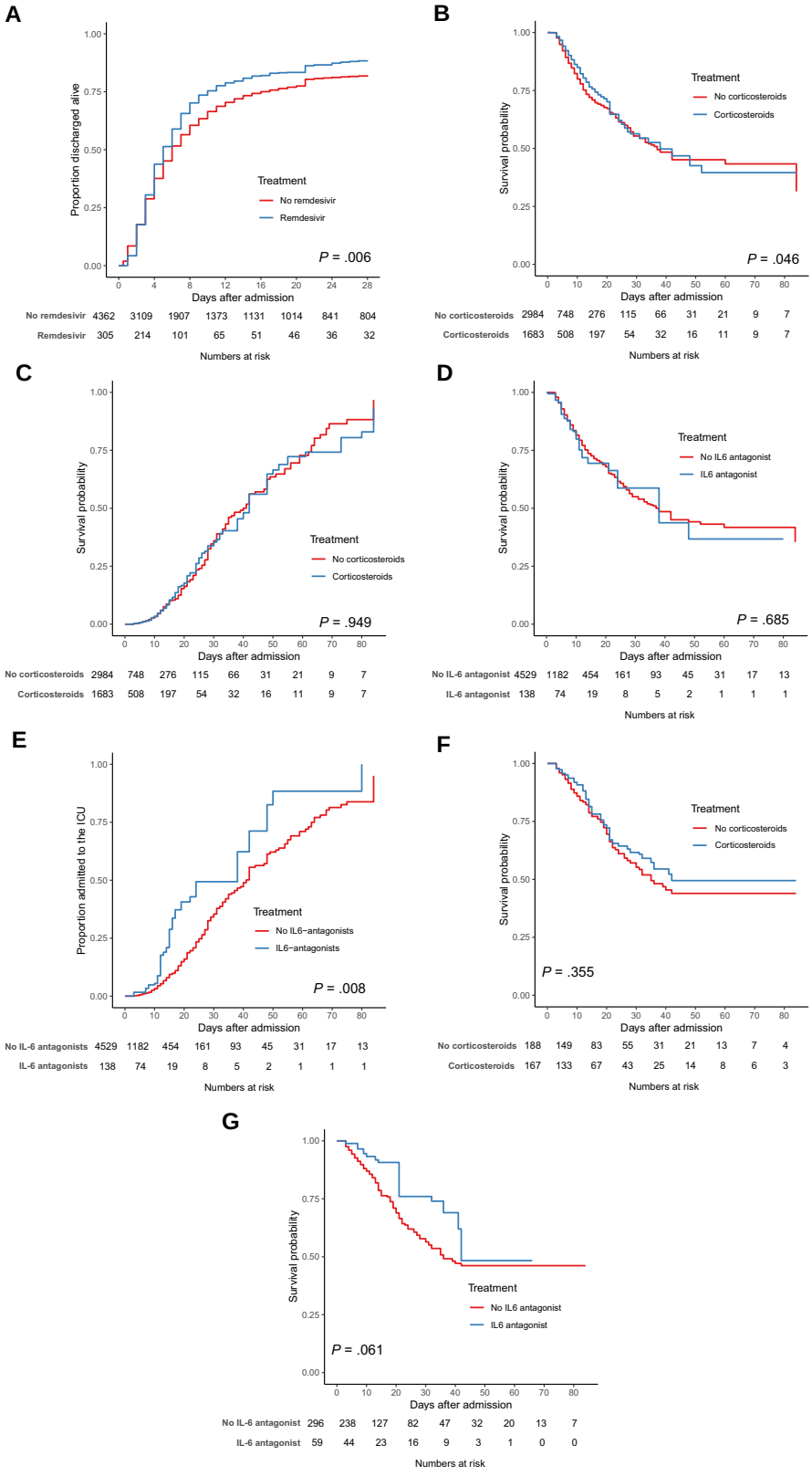

Figure 3. Effect of treatment in hospitalized COVID-19 patients of remdesivir (A), corticosteroids (B, C, F), and IL-6 antagonists (D, E, G) in patients directly admitted to the ward (A–E) and the ICU (F, G) in the propensity-weighted cohort. The treatment effect of remdesivir on discharge alive within 29 days is shown in patients directly admitted to the ward (A); the treatment effect of corticosteroids on in-hospital (B) and ICU admission (C) is shown in patients directly admitted to the ward, as well as the treatment effect of IL-6 antagonists on in-hospital (D) and ICU admission (E) in patients directly admitted to the ward. The treatment effect of corticosteroids (F) and IL-6 antagonists (G) is shown in patients directly admitted to the ICU. Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IL, interleukin.

younger patients per wave and lower in-hospital mortality for patients directly admitted to the ward. In our cohort of hospitalized patients, we only found positive associations of remdesivir and corticosteroids with the rate of being discharged alive within 29 days and, respectively, the in-hospital and 12-week mortality in patients directly admitted to the ward. Given the ongoing evolution of the SARS-CoV-2 virus with novel, clinically significant mutations appearing at a steady state during changing patient characteristics over time, it is essential to continuously re-evaluate the real-world effectiveness of newly introduced drugs to treat COVID-19.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Data sharing. The data that support the findings of this study are available from the corresponding author (M.S.) upon reasonable request.

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