Electronic Supplementary Material

Corticosteroids in H1N1, non-viral, and COVID-19 ARDS: a nationwide cohort study

Intensive Care Medicine

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eFig. 2 Survival from hospital admission to day 180

eFig. 3 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to the duration of use (<6 days vs ≥6 days) in H1N1, non-viral, or COVID-19 ARDS

eFig. 4 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to subgroup in H1N1 ARDS

eFig. 5 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to subgroup in non-viral ARDS

eFig. 6 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to subgroup in COVID-19 ARDS

eMethods

Study design and data source

This nationwide population-based study retrieved data from the Korean National Health Insurance Service (NHIS) database to construct (1) 2009 influenza A (H1N1) acute respiratory distress syndrome (ARDS) cohort (May 2009–April 2010), (2) non-viral ARDS cohort (January 2015–April 2019), and (3) coronavirus disease 2019 (COVID-19) ARDS cohort (January–December 2020). The study protocol for analysis of de-identified patient data was exempted from review by the Institutional Review Board of Chung-Ang University (1041078-202007-HR-180-01).

The NHIS database consists of reimbursement claims from all citizens who reside in Korea except for medical aid beneficiaries and healthcare beneficiaries for veterans (over 97% of the population in 2018) [1]. The data provide detailed information including demographics, diagnoses, prescriptions, procedures, discharge outcome, and date of death. The diagnostic codes were based on the International Classification of Diseases, 10th Revision (ICD-10). All prescribed and dispensed drugs were identified using Anatomical Therapeutic Chemical codes and the Korean Health Insurance Review and Assessment Service charge codes. Data were extracted by an independent technician at the NHIS center.

Study population

For H1N1 cases, patients with the ICD-10 codes for influenza (J09, J10, or J11) from May 2009 to April 2010 were included. The study period included the peak of the pandemic; thus, almost all influenza cases were presumed to be caused by the H1N1 strain [2]. Patients with non-viral ARDS were identified using the ICD-10 code for ARDS (J80) while excluding the codes for influenza (J09–J11) and viral pneumonia (J12) from January 2015 to April 2019. COVID-19 cases were identified using the ICD-10 codes, which were given only for confirmed COVID-19 cases based on positive nasopharyngeal swab specimens tested using real-time reverse transcription-polymerase chain reaction assays [3], from January to December 2020. For patients with multiple admissions for ARDS treatment, only the first admission was included. Patients were excluded if they were <18 years, died or were discharged within the

first two days of hospitalization, did not receive mechanical ventilation, were pregnant or had a related condition, were receiving palliative care, or experienced cardiac arrest. All patients were followed until death or 180 days following the day of hospital admission.

Corticosteroids

Corticosteroid use was defined as at least one dose for intravenous (IV) dexamethasone, hydrocortisone, or methylprednisolone during the hospitalization. If two or three different corticosteroids were used, the one with higher potency was selected for grouping. All doses were converted to methylprednisolone equivalents [4], and the cumulative dose and total duration of use were calculated. The detailed types and codes for IV corticosteroids are shown in eAppendix 1.

Data collection, definitions, and outcomes

Baseline patient characteristics included age, sex, Charlson comorbidities [5] defined on the basis of claim codes within one year before admission (eAppendix 2), immunosuppression (malignancies, human immunodeficiency virus infection, organ transplantation, or administration of immunosuppressive therapy), and previous steroid use (oral or IV for ≥30 days during the previous year). The hospital type was determined according to the number of beds and specialties (eAppendix 3), and the type of organ dysfunction was identified using ICD-10 codes (eAppendix 4). Vasopressor use was defined as the administration of norepinephrine, epinephrine, vasopressin, dopamine, or dobutamine during the hospitalization. Procedure codes were used to retrieve cases that involved renal replacement therapy and extracorporeal membrane oxygenation (ECMO).

The primary outcomes were 30- and 180-day mortality. The secondary outcomes included vasopressor days, ventilator days, intensive care unit (ICU) and hospital lengths of stay, and tracheostomy.

Statistical analysis

Data are presented as the mean (standard deviation) or median (interquartile range) for continuous variables and as numbers (percentages) for categorical variables. Continuous variables were compared using one-way ANOVA or the Kruskal-Wallis test, as appropriate, whereas categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

In logistic regression analyses, previous steroid use showed a high collinearity with immunosuppression and was excluded in the final model. Similarly, vasopressor use and renal replacement therapy revealed high collinearity with organ dysfunction and were excluded. The cutoff values for dosage of and duration of treatment with corticosteroids were based on Youden's index [6]. Randomized trials have shown a significant survival benefit of long-term corticosteroids in COVID-19 and non-COVID-19 ARDS [7, 8]. Thus, as a sensitivity analysis, the associations between corticosteroid use and mortality with stratification according to the duration of use (<6 days vs ≥6 days) were also analyzed.

No missing values were found in the dataset. The results of the secondary analyses should be considered hypothesis-generating due to the potential for type I error caused by multiple comparisons. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC, USA). All tests were two-tailed, and differences were considered statistically significant at $p < 0.05$.

eResults

Clinical outcomes

Patients with non-viral ARDS demonstrated significantly higher 30- (44.2% vs 29.4% vs 28.0%; $p < 0.001$) and 180-day mortality (67.2% vs 52.6% vs 49.2%; $p < 0.001$) than those with H1N1 or COVID-19 ARDS (eTable 2). The patients also demonstrated significantly more vasopressor and ventilator days, longer ICU and hospital lengths of stay, and a higher tracheostomy rate. The survival curves for the three cohorts are shown in eFig. 2.

Associations of the dosage of, duration of treatment with, and type of steroids with mortality

In H1N1 ARDS, a cumulative steroid dose ≥250 mg, steroid use for ≥3 days, and dexamethasone use were significantly associated with decreased 30-day mortality; however, these findings were not observed for 180-day mortality (Fig. 1). Methylprednisolone was associated with a significantly increased risk of 180-day mortality. Among patients with non-viral ARDS, corticosteroid use (regardless of dosage) for ≥3 days and dexamethasone use were significantly associated with decreased 30- and 180-day mortality (Fig. 1). Hydrocortisone use was associated with a significantly increased risk of 180-day mortality. In COVID-19 ARDS, corticosteroid use (regardless of dosage and duration), dexamethasone use, and methylprednisolone use were significantly associated with decreased 30-day mortality but not with decreased 180-day mortality (Fig. 1). A cumulative steroid dose ≥250 mg, steroid use for ≥3 days, hydrocortisone use, and methylprednisolone use were associated with a significantly increased risk of 180-day mortality. These observations did not change substantially when the analyses were stratified according to corticosteroid use for <6 days vs ≥6 days (eFig. 3).

Subgroup analyses

In H1N1 ARDS, corticosteroid use was associated with a significantly lower risk of 30-day mortality in older patients (≥65 years) with less organ dysfunction (<3); however, these findings were not observed for 180-day mortality (eFig. 4). A significantly increased risk of 180-day mortality was observed in younger patients (<65 years). No significant interaction was

observed with any variable among patients with non-viral ARDS (eFig. 5). In COVID-19 ARDS, the associations between corticosteroid use and 30-day mortality were not influenced when the patients were stratified according to any variable (eFig. 6). However, corticosteroid use was significantly associated with increased 180-day mortality in patients with less organ dysfunction and immunosuppression.

eDiscussion

The present study revealed three main findings. First, corticosteroid use was protective for 30- and 180-day mortality in non-viral ARDS. However, corticosteroid use was only protective for 30-day mortality in viral ARDS. Furthermore, long-term corticosteroids were associated with increased 180-day mortality among patients with COVID-19 ARDS. Second, dexamethasone was associated with decreased 30- and 180-day mortality in viral and non-viral ARDS. Third, there was an increased risk of 180-day mortality with corticosteroid use among patients with COVID-19 ARDS who had less organ dysfunction and immunosuppression.

Corticosteroid use was associated with decreased 30-day mortality among patients with H1N1 ARDS. This might be explained by the findings that relatively low-dose steroids (approximately 60 mg/day of methylprednisolone equivalents) were administered, and all patients were mechanically ventilated. Previous reports showed that low-to-moderate-dose corticosteroids reduced mortality among severe H1N1 patients with a PaO_2/FiO_2 <300 mmHg [9]. Notably, corticosteroids were associated with both decreased 30- and 180-day mortality in non-viral ARDS but were not associated with decreased 180-day mortality in H1N1 or COVID-19 ARDS. The differences in complications from corticosteroid use, such as nosocomial infection and muscle weakness, between viral and non-viral ARDS might influence long-term morbidity and mortality. Additional studies are required to address this issue.

The optimal dosage of steroid therapy in ARDS remains unknown. The present results showed that corticosteroids were generally associated with decreased 30-day mortality among all patients with ARDS, regardless of dosage. These findings are in accordance with those of a recent meta-analysis suggesting that the effect of corticosteroids on mortality in ARDS appears to be consistent between different dosages [10].

Dexamethasone was associated with decreased 30-day mortality among all patients with ARDS, and the survival benefits continued with a follow-up duration of 180 days. Dexamethasone has the highest binding affinity to the glucocorticoid receptor [11]. In addition, the effective dose and half-life of dexamethasone are higher than those of other corticosteroids [12]. Moreover, multicenter randomized trials have used dexamethasone to reduce the duration of mechanical ventilation and mortality in COVID-19 and non-COVID-19 ARDS [7, 8]. Conversely, methylprednisolone was associated with increased 180-day mortality in H1N1 or

COVID-19 ARDS. These findings may be unexpected given the higher lung penetration of methylprednisolone than dexamethasone [13]. Further studies are needed to explore the long-term safety of methylprednisolone for ARDS.

Corticosteroids may be beneficial or harmful in certain ARDS phenotypes. In H1N1 ARDS, corticosteroid use was associated with a decreased risk of 30-day mortality in patients with older age but was associated with an increased risk of 180-day mortality in younger age. In COVID-19 ARDS, corticosteroid use was associated with increased 180-day mortality in patients with less organ dysfunction. Consistent findings were observed in the Metcovid trial, which found a significantly lower 28-day mortality in older patients (>60 years) with COVID-19 with higher C-reactive protein levels who received methylprednisolone [14]. In addition, a recent study of critically ill patients with COVID-19 showed that corticosteroids were associated with decreased 90-day mortality in those with more severe illness [15]. Taken together, these findings suggest that corticosteroids might benefit patients who are elderly or have a more severe inflammatory response.

To the best of our knowledge, the current study is one of the few epidemiologic studies to evaluate whether corticosteroid use was associated with mortality in a nationwide cohort of ARDS due to different etiologies. The main strength of study is the long-term (180 days) data from a substantial number of patients with comparison groups. Various subgroup analyses were also performed to identify ARDS phenotypes more likely to benefit from corticosteroids. Controversies exist between the findings of previous studies and the present results regarding the use of corticosteroids, especially methylprednisolone, and increased long-term mortality in COVID-19 ARDS. However, it should be noted that most previous studies that showed a survival benefit limited follow-up to 28 days.

This study has several limitations. First, its retrospective nature cannot exclude the likelihood of residual confounding and precludes causal inference on association between corticosteroid use and mortality. Second, the accuracy of diagnostic codes for ARDS may be limited by the possibility of over- or undercoding. For H1N1 or COVID-19 ARDS, it was not feasible to include patients who met the Berlin definition [16] because chest imaging and oxygenation data were lacking. However, the current study only included patients who received mechanical ventilation, and viral infections with severe respiratory failure usually present with

bilateral infiltrates [17]. Third, vital signs and laboratory data were also lacking, but diagnoses, prescriptions, and procedures served as surrogates for ARDS severity. Logistic regression model for mortality included organ dysfunction and ECMO as covariates. However, adjusting for these variables may induce a risk of overcorrection on factors which could be intermediates between the exposure and the outcome [18]. Fourth, data on the timing of corticosteroid initiation were unavailable due to lack of time stamps. Thus, whether early or late treatment is associated with outcomes could not be assessed. Patients who died or were discharged within two days of hospitalization were excluded to minimize immortal time bias. Fifth, the standard of care in ARDS, such as ventilation parameters and rescue therapies, may have changed between 2009 and 2020, and these may have biased the results. Sixth, important patient outcomes other than mortality, including health-related quality of life and functional/cognitive/neurologic outcomes, were not studied.

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eAppendix 1 Types and codes for intravenous corticosteroids

Variable	ATC codes	HIRA charge codes
Dexamethasone		
Dexamethasone palmitate 4 mg	H02AB02	142001BIJ
Dexamethasone palmitate 4 mg	H02AB02	142030BIJ
Dexamethasone sodium phosphate 5 mg	H02AB02	142201BIJ
Dexamethasone sodium phosphate 4.37 mg	H02AB02	142202BIJ
Dexamethasone disodium phosphate 4.37 mg	H02AB02	142230BIJ
Dexamethasone disodium phosphate 5 mg	H02AB02	142232BIJ
Dexamethasone disodium phosphate 20 mg	H02AB02	142233BIJ
Hydrocortisone		
Hydrocortisone sodium succinate 100 mg	H02AB09	171201BIJ
Hydrocortisone sodium succinate 250 mg	H02AB09	171202BIJ
Methylprednisolone		
Methylprednisolone acetate 200 mg	H02AB04	193501BIJ
Methylprednisolone acetate 40 mg	H02AB04	193502BIJ
Methylprednisolone acetate 40 mg	H02AB04	193530BIJ
Methylprednisolone acetate 200 mg	H02AB04	193531BIJ
Methylprednisolone sodium succinate 125 mg	H02AB04	193601BIJ
Methylprednisolone sodium succinate 250 mg	H02AB04	193602BIJ
Methylprednisolone sodium succinate 40 mg	H02AB04	193603BIJ
Methylprednisolone sodium succinate 500 mg	H02AB04	193604BIJ

ATC Anatomic Therapeutic Chemical; *HIRA* Health Insurance Review and Assessment Service

eAppendix 2 Comorbidities based on the Charlson Comorbidity Index[a]

Variable	ICD-10 codes
Charlson Comorbidity Index	
Myocardial infarction	I21, I22, I252
Congestive heart failure	I099, I110, I130, I132, I255, I420, I425, I426, I427, I428, I429, I43, I50, P290
Peripheral vascular disease	I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959
Cerebrovascular disease	G45, G46, I60, I61, I62, I63, I64, I65, I66, I67, I68, I69, H340
Dementia	F00, F01, F02, F03, G30, F051, G311
Chronic pulmonary disease	I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703
Rheumatic disease	M05, M06, M315, M32, M33, M34, M351, M353, M360
Peptic ulcer disease	K25, K26, K27, K28
Mild liver disease	B18, K700, K701, K702, K703, K709, K713, K714, K715, K717, K73, K74, K760, K762, K763, K764, K768, K769, Z944
Moderate or severe liver disease	I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767
Diabetes without complications	E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149
Diabetes with complications	E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147
Paraplegia and hemiplegia	G041, G114, G800, G81, G82, G830, G831, G832, G833, G834, G839
Renal disease	I120, I131, N030, N031, N032, N033, N034, N035, N036, N037, N038, N039, N050, N051, N052, N053, N054, N055, N056, N057, N058, N059, N18, N19, N250, Z490, Z491, Z492, Z940, Z992
Any malignancy	C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97
Metastatic solid tumor	C77, C78, C79, C80
AIDS/HIV	B20, B21, B22, B24
Hypertension, uncomplicated	I10
Hypertension, complicated	I11, I12, I13, I15

AIDS acquired immune deficiency syndrome; *HIV* human immunodeficiency virus; *ICD* International Classification of Diseases

[a] Hypertension is included as a Charlson comorbidity and was identified separately using the ICD-10 codes

eAppendix 3 Hospital types defined by Korean Health Law according to the number of beds and specialties

Public health center

General practitioner

Hospital: healthcare institution with >30 inpatient beds

General hospital: hospital with >100 beds and >7 specialty departments for internal medicine, surgery, pediatrics, obstetrics and gynecology, anesthesiology, pathology, and laboratory medicine

Tertiary hospital: general hospital with >20 specialty departments that serves as a teaching hospital for medical students and nurses

eAppendix 4 ICD-10-based classification of organ dysfunction

Variable	Codes
Cardiovascular	
Septic shock	R572
Hypotension	I95
Other hypotension	I958
Hypotension, unspecified	I959
Shock, NEC	R57
Other shock	R578
Shock, unspecified	R579
Shock (endotoxic, hypovolemic) during or following a procedure	T811
Use of a vasopressor (norepinephrine, epinephrine, vasopressin, dopamine)	
Respiratory	
Adult respiratory distress syndrome	J80
Pulmonary edema	J81
Respiratory failure, NEC	J96
Acute respiratory failure	J960
Respiratory failure, unspecified	J969
Hypoxemia	R0902
Cyanosis	R230
Dependence on respirator	Z991
Conventional oxygen therapy, high-flow nasal cannula, mechanical ventilation	
Neurologic	
Delirium not induced by alcohol and other psychoactive substances	F05
Other mental disorders due to brain damage and dysfunction and to physical disease	F06
Organic psychosis NOS	F09
Anoxic brain damage, NEC	G931
Encephalopathy, unspecified	G934
Metabolic encephalopathy	G9380
Somnolence, stupor and coma	R40
Somnolence	R400
Stupor	R401
Disorientation, unspecified	R410
Hematologic	
Disseminated intravascular coagulation (defibrination syndrome)	D65
Other coagulation defects	D68
Other specified coagulation defects	D688
Coagulation defect, unspecified	D689
Purpura and other hemorrhagic conditions	D69
Secondary thrombocytopenia	D695
Thrombocytopenia, unspecified	D696
Spontaneous ecchymoses	R233
Abnormal coagulation lab	R791
Hepatic	
Hepatic failure, NEC	K72
Central hemorrhagic necrosis of liver	K762
Infarction of liver	K763
Unspecified jaundice	R17
Renal	
Acute renal failure	N17
Unspecified renal failure	N19
Postprocedural renal failure	N990
Anuria and oliguria	R34
Abnormal results of kidney function studies	R944

Variable	Codes
Dependence on renal dialysis	Z992
Renal replacement therapy	
Metabolic	
Acidosis	E872

ICD International Classification of Diseases; *NEC* not elsewhere classified; *NOS* not otherwise specified

eTable 1 Baseline patient characteristics in H1N1, non-viral, or COVID-19 ARDS

Characteristics	H1N1 (n = 3461)	Non-viral (n = 6862)	COVID-19 (n = 7783)	*p* value
Age, mean (SD), y	64.6 (15.1)	67.8 (14.5)	68.4 (14.5)	<0.001
Sex, No. (%)				0.03
Male	2148 (62)	4418 (64)	4878 (63)	
Female	1313 (38)	2444 (36)	2905 (37)	
Comorbidities, No. (%)				
Diabetes	1543 (45)	2887 (42)	3609 (46)	<0.001
Hypertension	2095 (61)	4243 (62)	5308 (68)	<0.001
Myocardial infarction	230 (7)	320 (5)	483 (6)	<0.001
Congestive heart failure	559 (16)	1376 (20)	2145 (28)	<0.001
Cerebrovascular disease	1041 (30)	1868 (27)	2388 (31)	<0.001
Chronic pulmonary disease	1837 (53)	3700 (54)	3974 (51)	0.002
Chronic liver disease	1093 (32)	2725 (40)	3145 (40)	<0.001
Chronic kidney disease	358 (10)	713 (10)	1286 (17)	<0.001
Malignancy	708 (20)	1718 (25)	1883 (24)	<0.001
Charlson Comorbidity Index, mean (SD)	3.1 (2.9)	3.2 (2.9)	3.6 (3.1)	<0.001
Immunosuppression, No. (%)[a]	1462 (42)	3382 (49)	3509 (45)	<0.001
Previous steroid use, No. (%)[b]	1939 (56)	4195 (61)	4512 (58)	<0.001
Organ dysfunction, No. (%)				
Cardiovascular	2705 (78)	6341 (92)	6667 (86)	<0.001
Respiratory	3461 (100)	6862 (100)	7783 (100)	<0.001
Neurologic	223 (6)	322 (5)	397 (5)	<0.001
Hematologic	668 (19)	1687 (25)	1062 (14)	<0.001
Hepatic	9 (0.3)	79 (1)	25 (0.3)	<0.001
Renal	427 (12)	2002 (29)	1650 (21)	<0.001
Metabolic	138 (4)	567 (8)	357 (5)	<0.001
No. of organ dysfunctions, No. (%)				
1	596 (17)	396 (6)	904 (12)	<0.001
2	1852 (54)	3248 (47)	4318 (55)	<0.001
3	758 (22)	2128 (31)	1925 (25)	<0.001
≥4	255 (7)	1090 (16)	636 (8)	<0.001
Corticosteroids, No. (%)	1969 (57)	5171 (75)	4866 (63)	<0.001
Dexamethasone	623 (32)	1883 (36)	1817 (37)	<0.001
Hydrocortisone	445 (23)	906 (18)	1153 (24)	<0.001
Methylprednisolone	901 (46)	2382 (46)	1896 (39)	<0.001
Cumulative dose, median (IQR), mg[c]	125 (40–396)	180 (60–570)	125 (40–400)	<0.001
Total days of use, median (IQR)	2 (1–4)	3 (1–7)	2 (1–5)	<0.001
Neuromuscular blocking agents, No. (%)	1472 (43)	4262 (62)	4410 (57)	<0.001
Total days of use, median (IQR)	1 (1–2)	1 (1–2)	1 (1–1)	<0.001
Vasopressor use, No. (%)	2696 (78)	6292 (92)	6610 (85)	<0.001
Renal replacement therapy, No. (%)	383 (11)	1778 (26)	1516 (19)	<0.001
ECMO, No. (%)	16 (0.5)	126 (1.9)	50 (0.6)	<0.001

ARDS acute respiratory distress syndrome; *COVID-19* coronavirus disease 2019; *ECMO* extracorporeal membrane oxygenation; *H1N1* 2009 influenza A

[a] Immunosuppression includes malignancies, human immunodeficiency virus infection, organ transplantation, or administration of immunosuppressive therapy

[b] Defined by oral or intravenous for ≥30 days during the previous year

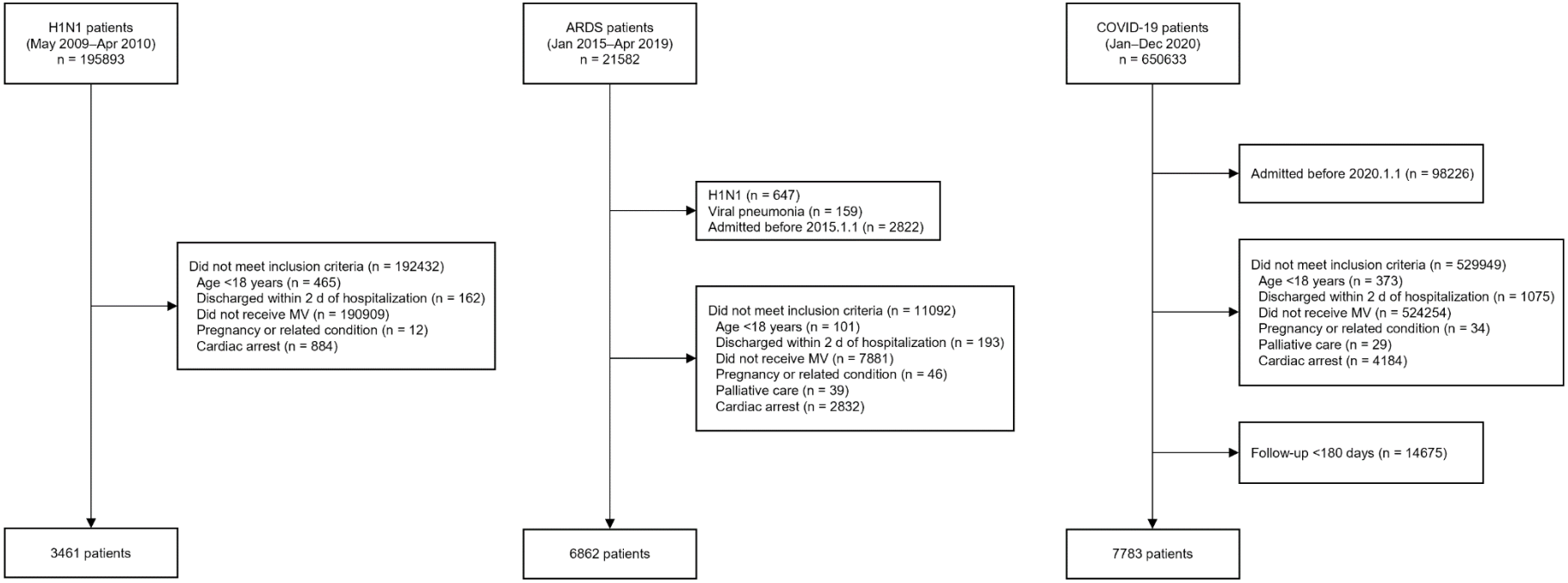
[c] Total cumulative dose was calculated as the sum of methylprednisolone doses and converted doses of dexamethasone and hydrocortisone

eTable 2 Primary and secondary outcomes

Outcomes	H1N1 (n = 3461)	Non-viral (n = 6862)	COVID-19 (n = 7783)	*p* value
Primary outcomes				
30-day mortality, No. (%)	1019 (29.4)	3035 (44.2)	2181 (28.0)	<0.001
180-day mortality, No. (%)	1821 (52.6)	4614 (67.2)	3828 (49.2)	<0.001
Secondary outcomes				
Vasopressor days, median (IQR)	1 (1–3) [n = 2696]	2 (1–3) [n = 6292]	1 (1–3) [n = 6610]	<0.001
Ventilator days, median (IQR)	2 (1–8)	5 (1–13)	2 (1–6)	<0.001
Length of stay, median (IQR), days				
ICU	8 (3–15)	11 (4–21)	6 (2–15)	<0.001
Hospital	29 (14–61)	39 (17–614)	29 (14–77)	<0.001
Tracheostomy, No. (%)	580 (17)	1584 (23)	1343 (17)	<0.001

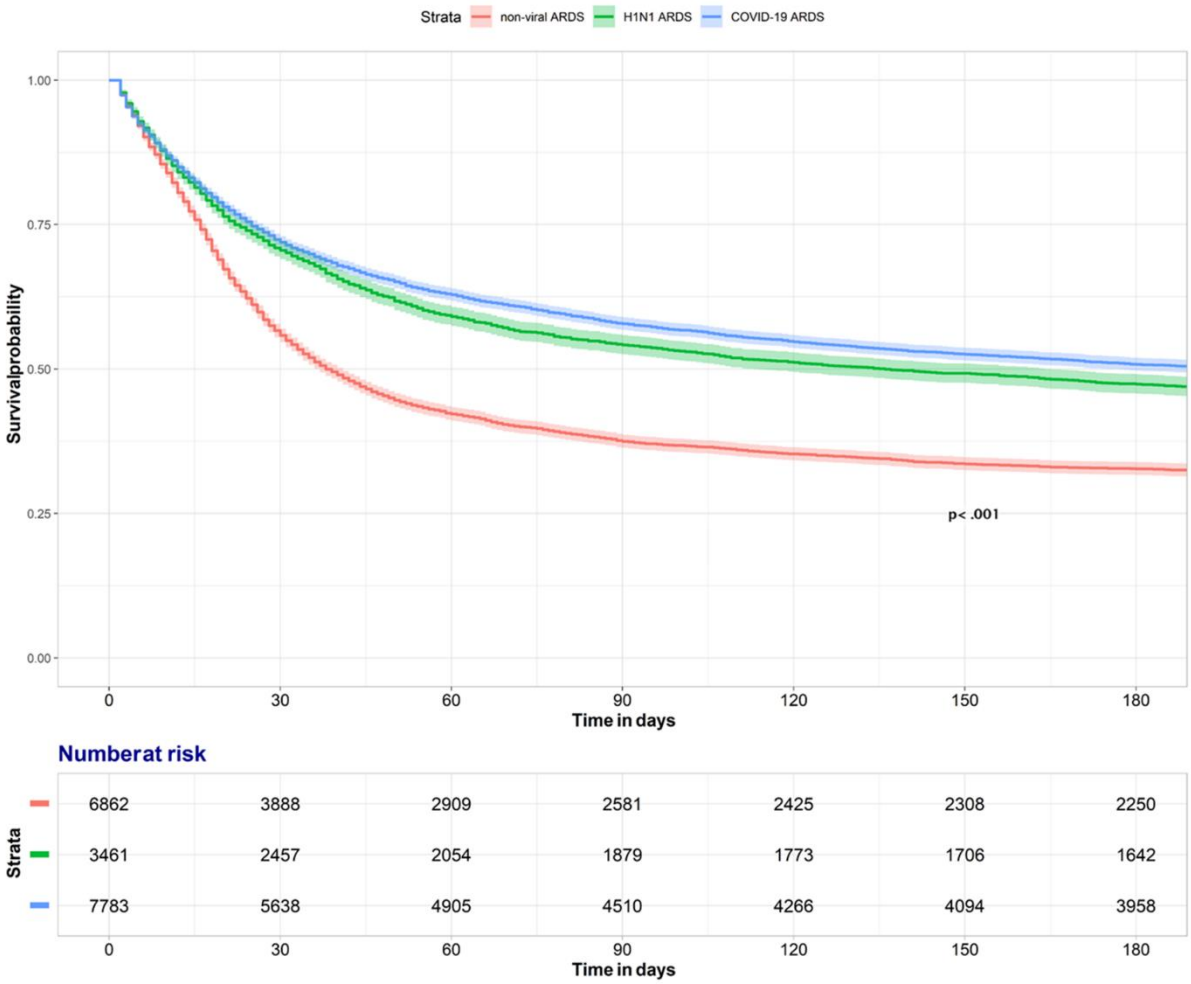
ARDS acute respiratory distress syndrome; *COVID-19* coronavirus disease 2019; *H1N1* 2009 influenza A; *ICU* intensive care unit

eFig. 1 Patient inclusion flowchart in the nationwide cohort study of H1N1, non-viral, and COVID-19 ARDS



ARDS acute respiratory distress syndrome; *COVID-19* coronavirus disease 2019; *H1N1* 2009 influenza A; *MV* mechanical ventilation

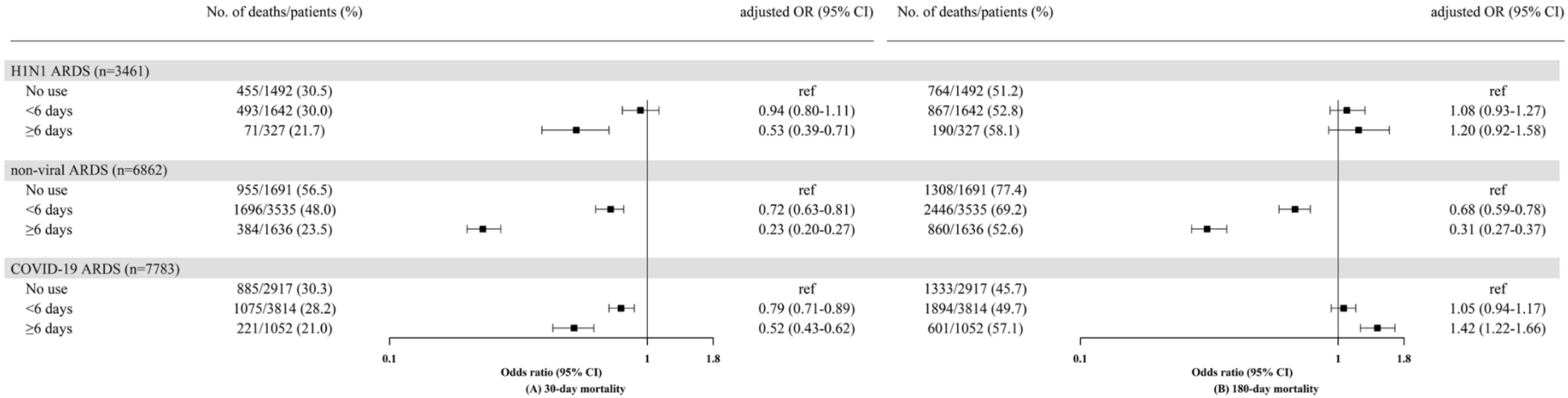
eFig. 2 Survival from hospital admission to day 180



The median (interquartile range) time to death was 61 (17–488) days in H1N1 ARDS, 26 (12–65) days in non-viral ARDS, and 27 (10–72) days in COVID-19 ARDS

ARDS acute respiratory distress syndrome; *COVID-19* coronavirus disease 2019; *H1N1* 2009 influenza A

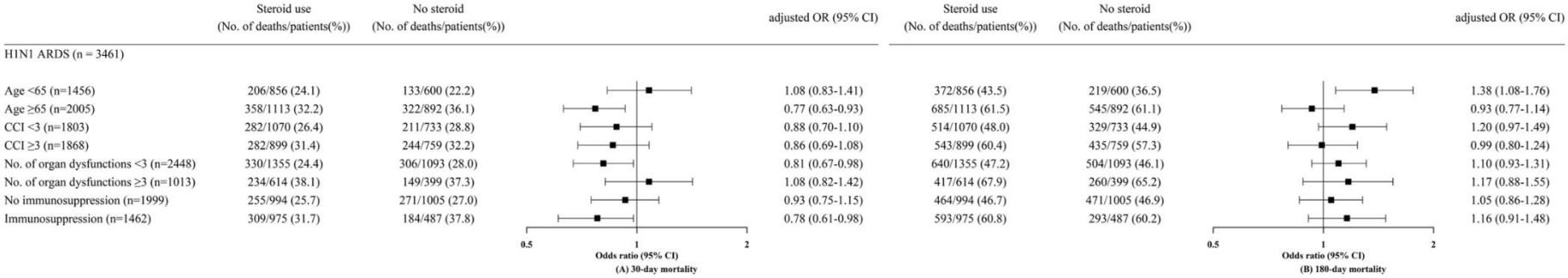
eFig. 3 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to the duration of use (<6 days vs ≥6 days) in H1N1, non-viral, or COVID-19 ARDS



The numbers and percentages of patients who died according to each risk factor and the resulting odds ratios, adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, hospital type, organ dysfunction, neuromuscular blocking agent use, and extracorporeal membrane oxygenation

ARDS acute respiratory distress syndrome; *COVID-19* coronavirus disease 2019; *H1N1* 2009 influenza A

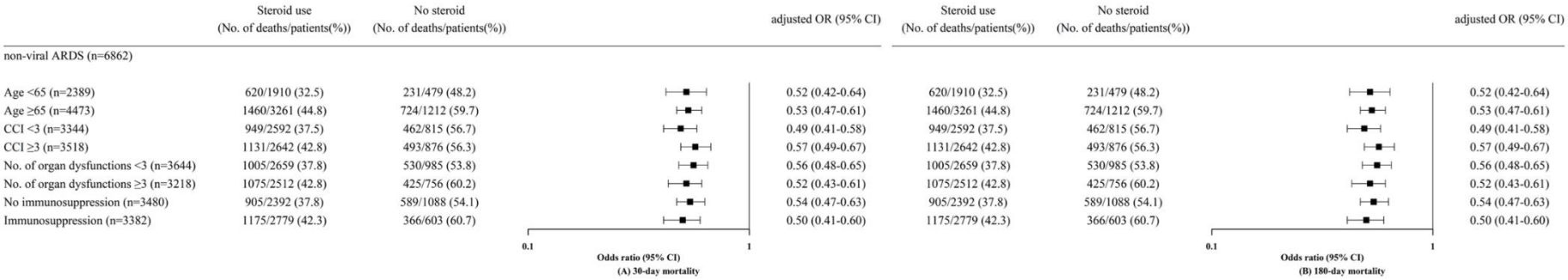
eFig. 4 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to subgroup in H1N1 ARDS



The numbers and percentages of patients who died according to each subgroup and the resulting odds ratios, adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, hospital type, organ dysfunction, neuromuscular blocking agent use, and extracorporeal membrane oxygenation

ARDS acute respiratory distress syndrome; *CCI* Charlson Comorbidity Index; *H1N1* 2009 influenza A

eFig. 5 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to subgroup in non-viral ARDS

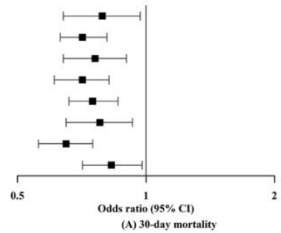


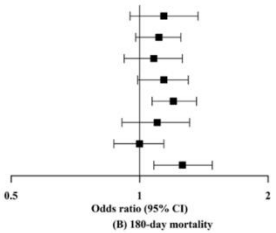
The numbers and percentages of patients who died according to each subgroup and the resulting odds ratios, adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, hospital type, organ dysfunction, neuromuscular blocking agent use, and extracorporeal membrane oxygenation

ARDS acute respiratory distress syndrome; *CCI* Charlson Comorbidity Index

eFig. 6 Associations between corticosteroid use and **(A)** 30- and **(B)** 180-day mortality according to subgroup in COVID-19 ARDS

	Steroid use (No. of deaths/patients(%))	No steroid (No. of deaths/patients(%))	adjusted OR (95% CI)	Steroid use (No. of deaths/patients(%))	No steroid (No. of deaths/patients(%))	adjusted OR (95% CI)
COVID-19 ARDS (n=7783)						
Age <65 (n=2736)	348/1660 (21.0)	237/1076 (22.0)	0.79 (0.64-0.97)	643/1660 (38.7)	337/1076 (31.3)	1.14 (0.95-1.37)
Age ≥65 (n=5047)	948/3206 (29.6)	648/1841 (35.2)	0.71 (0.63-0.81)	1852/3206 (57.8)	996/1841 (54.1)	1.11 (0.98-1.25)
CCI <3 (n=3396)	493/2069 (23.8)	359/1327 (27.1)	0.76 (0.64-0.90)	890/2069 (43.0)	517/1327 (39.0)	1.08 (0.92-1.26)
CCI ≥3 (n=4387)	803/2797 (28.7)	526/1590 (33.1)	0.71 (0.61-0.82)	1605/2797 (57.4)	816/1590 (51.3)	1.14 (0.99-1.30)
No. of organ dysfunctions <3 (n=5222)	664/3119 (21.3)	542/2103 (25.8)	0.75 (0.66-0.86)	1386/3119 (44.4)	836/2103 (39.8)	1.20 (1.07-1.36)
No. of organ dysfunctions ≥3 (n=2561)	632/1747 (36.2)	343/814 (42.1)	0.78 (0.65-0.93)	1109/1747 (63.5)	497/814 (61.1)	1.10 (0.91-1.31)
No immunosuppression (n=4274)	551/2384 (23.1)	549/1890 (29.1)	0.65 (0.56-0.75)	1093/2384 (45.9)	823/1890 (43.5)	1.00 (0.87-1.14)
Immunosuppression (n=3509)	745/2482 (30.0)	336/1027 (32.7)	0.83 (0.71-0.98)	1402/2482 (56.5)	510/1027 (49.7)	1.26 (1.08-1.48)





The numbers and percentages of patients who died according to each subgroup and the resulting odds ratios, adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, hospital type, organ dysfunction, neuromuscular blocking agent use, and extracorporeal membrane oxygenation

ARDS acute respiratory distress syndrome; *CCI* Charlson Comorbidity Index; *COVID-19* coronavirus disease 2019