

Adaptation of the WHO COVID-19 Clinical Progression Scale for Registry-Based Data: A Whole-Population Study in Sweden

Hanna Jerndal¹, Sebastian Kalucza¹, Frida Jakobsson¹, Anders Hviid^{2,3}, Tyra Grove Krause², Clas Ahlm¹, Johan Normark¹, Osvaldo Fonseca-Rodríguez¹, Marie Eriksson⁴, Anne-Marie Fors Connolly¹

¹Department of Clinical Microbiology, Umeå University, Umeå, SE 901 85, Sweden; ²Epidemiological Infectious Disease Preparedness, Statens Serum Institut, Copenhagen, 2300, Denmark; ³Department of Drug Development and Pharmacology, University of Copenhagen, Copenhagen, 2100, Denmark; ⁴Department of Statistics, USBE, Umeå University, Umeå, SE 901 87, Sweden

Correspondence: Anne-Marie Fors Connolly, Department of Clinical Microbiology, Umeå University, Umeå, SE 901 85, Sweden, Email anne-marie.fors.connolly@umu.se

Purpose: COVID-19 has been extensively researched; however, the lack of standardized COVID-19 severity categorization in register-based research complicates comparison of studies. The WHO COVID-19 Clinical Progression Scale is a standardized disease severity tool for clinical data, though not adapted to data available in health registries. We aimed to develop and validate such a novel categorization with international applicability.

Methods: The WHO Clinical Progression Scale was translated to a severity index utilizing ICD- and procedure-codes from outpatient, inpatient, intensive care, and mortality registries using the adult Swedish population and SARS-CoV-2 positive-test data (January 2020 – July 2022). Cox proportional hazards were applied to determine whether increasing severity correlates with mortality in COVID-19 patients compared to the population.

Results: The WHO-Scale was translated to ten categories reflecting the increasing need for advanced care, encompassing 8,245,474 individuals including 1,981,946 SARS-CoV-2 infections. Fatal COVID-19 cases were older with more comorbidities. Those receiving mechanical ventilation and ECMO were younger with fewer comorbidities. Among survivors beyond 30 days, 90-day all-cause mortality increased with severity using category zero (no laboratory-verified SARS-CoV-2) as reference. Mortality was lowest for patients without health care adjusted for age, sex, comorbidities and socio-economic variables (adjusted hazard ratio (aHR) 1.18, 95% confidence interval (CI) 1.13–1.22). Those hospitalized >5 days had higher mortality (aHR 5.83, 5.5–6.17). Those requiring ECMO/ECLS had the highest mortality (aHR 593.54, 317.77–1108.65).

Conclusion: The novel COVID-19 severity index associated with all-cause 90-day mortality and aligned with previous literature. This index will enable comparative studies of COVID-19, which is important for public health policies and development of clinical guidelines. This is an innovative epidemiologic tool with potential applicability in all countries with centralised health registers. The index also has the potential to be used for other infectious diseases and in real-time data for modelling predictions.

Keywords: whole-population, disease severity index, standardization, infectious diseases, COVID-19, epidemiology

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was the second leading cause of death globally in 2021, resulting in an estimated 8.8 million deaths.¹ Though primarily considered a respiratory disease,² COVID-19 may impact several organ systems, such as cardiovascular functions, kidneys, liver, central nervous system, and the coagulation system.^{3–9}

To assess severity and predict risk in viral respiratory diseases, several clinical scoring systems are used. These include CURB-65 (confusion, uremia, respiratory rate, blood pressure, age ≥ 65 years),¹⁰ SOFA ('Sequential Organ

Failure Assessment),¹¹ PSI (Pneumonia Severity Index),¹² SIRS (Systemic Inflammatory Response Syndrome),¹³ APACHE II (Acute Physiology and Chronic Health Evaluation II),¹⁴ NEWS2 (National Early Warning Score 2),¹⁵ and the Clinical Progression Scale for COVID-19 defined by the World Health Organization (WHO).¹⁶ Disease severity is evaluated through symptoms, clinical signs, laboratory tests, radiological findings, required level of care, interventions and clinical outcomes.¹⁷ The WHO has defined a Clinical Progression Scale for COVID-19 studies to enable comparison of clinical studies.¹⁶ This scale was based on level of care, need of oxygen and organ support,¹⁶ which is not readily adaptable to registry data due to limited access to clinical data and limited information on treatment during hospitalization.^{16,18}

The Nordic countries have unique and extensive register data, which can be linked by each individual's personal identification number (PIN). This includes information on contacts with outpatient and inpatient clinics, causes of death, prescribed pharmaceuticals and others.^{19,20} In Sweden, all laboratory-verified positive SARS-CoV-2 tests are registered at the centralized communicable disease surveillance database SmiNet.²¹

Our objective was to adapt the WHO Clinical Progression Scale for COVID-19 severity¹⁶ for registry data and e-health records. We hypothesized that increasing disease severity correlates with poor clinical outcomes.

Materials and Methods

Study Population and Data Sources

Data for the Swedish population between January 1st 2020 and July 27th 2022 was retrieved from the Total Population Registry using PINs for every individual, administered by Statistics Sweden (Figure 1).²² Annual disposable income, education level, residence status and region of birth were obtained from Statistics Sweden's registries (1997–2021). The national registries provide nearly complete population coverage, as reporting of deaths and other health and socio-economic data is mandatory.²³ Individual data regarding laboratory-confirmed SARS-CoV-2 tests and COVID-19 vaccinations (SmiNet, a communicable disease surveillance database, and the COVID-19 Vaccination Registry^{21,24} January 2020 – July 2022); outpatient clinic visits (Outpatient Registry (OPR), 1997 to 2022), hospitalizations (Inpatient Registry 1987–2022), both administered by the National Board of Health and Welfare (NBHW),²⁵ intensive care unit (ICU) stays (Swedish Intensive Care Registry (SIR) 2020–2022),²⁶ registered cancers (Cancer Registry 1987–2022 NBHW),²⁷ causes of death (Cause of Death Registry 2020–2022 NBHW),²⁸ and need for elderly assistance or care home (SOL registry 2020–2022 NBHW).²⁹ All PINs were exchanged with study codes for pseudonymization by Statistics Sweden before the data was transferred to Umeå University for analysis.

Individuals without a registered residency since 2018 and/or missing data regarding income or education were excluded (Figure 1). Given the physiological differences in responses to SARS-CoV-2 and variations in clinical guidelines, only individuals aged 18 and above were included. Every individual in the Swedish population was assigned a random index date between January 1st and December 31st, followed for 365 days, with a new follow-up period starting the same date the following year.

Exposure – Laboratory Verified Positive SARS-CoV-2 Infection

Exposure was defined as laboratory-verified SARS-CoV-2 infection registered in SmiNet. The COVID-19 date was the first related entry in SmiNet, based on symptom onset, sample date, diagnosis, or report date (Supplementary Figure 1A and B). A person was considered a COVID-19 case from the COVID-19 date and for 365 days. If a new laboratory-verified positive test was registered in SmiNet after 6 months post previous COVID-19 date, the person was considered re-infected, with a new 365-day follow-up. After 365 days post-COVID-19, individuals were re-assigned to the non-infected group with their initial index date.

Development of COVID-19 Disease Severity Index for Registry Data

The WHO Clinical Progression Scale for COVID-19 severity¹⁶ was adapted for use with registry data by mapping categories to corresponding severity levels (Figure 2 and Supplementary Table 1). This adaptation incorporated International Classification of Disease (ICD) codes and medical procedure codes from the following Swedish

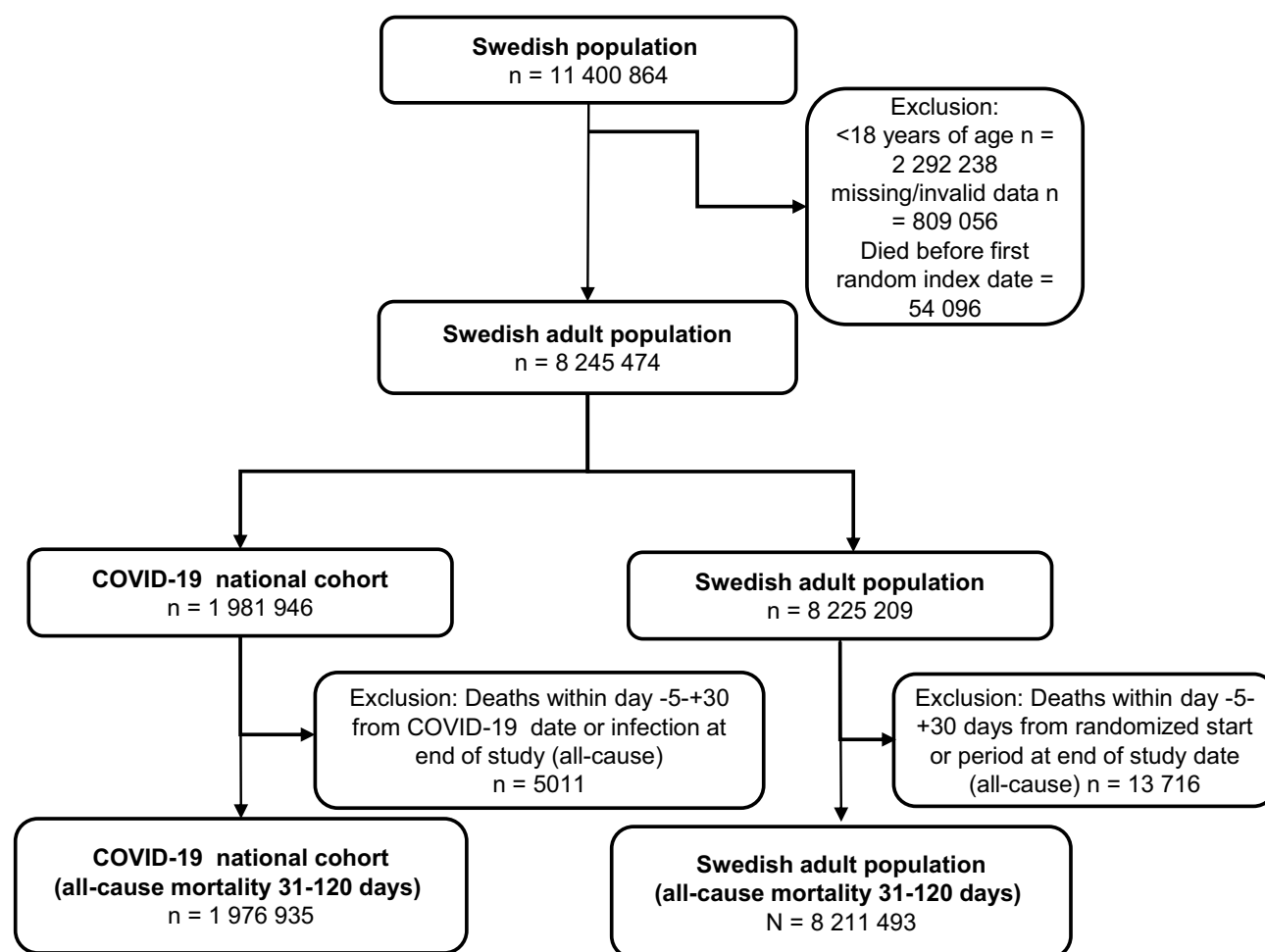


Figure 1 Flow diagram of study cohort. All adults in Sweden from January 1st 2020 to July 27th 2022 including those with a laboratory-verified positive SARS-CoV-2 test were included in this study. Individuals who died within -5 to +30 days from COVID-19 date or index date were excluded from the survival analysis day 31–120.

Outpatient, Inpatient, Intensive Care and Cause of Death registries. Classification was determined within a period of -5 days to +30 days after COVID-19 date, based on clinical experience the highest initial registered disease severity. The WHO Clinical Progression Scale for COVID-19 severity¹⁶ contains 11 categories, from 0 (not infected) to 10 (death from COVID-19). A new method was developed, to interpret and translate these categories into severity categories using data from the national health registries, including ICD-10 codes and medical procedure codes.

Covariates

The comorbidity burden was determined using the weighted Charlson Comorbidity Index (wCCI)³⁰ stratified into groups: 0 points (reference group), 1–2, 3–4 and 5 or more points. Age was stratified into the following categories: 18–49 years (reference group), 50–64 years, 65–79 years, 80 years or older. Vaccine status was categorized as follows: unvaccinated (reference group), first vaccination dose (and within three months of the first dose), first vaccination more than three months prior, two vaccine doses, and three or more doses.

Individuals were considered vaccinated 14 days after their first dose to account for the time needed for full protection, with a minimum 3-month interval between doses to prevent duplicate registrations. Proximity to health care, likely influencing timely access to care, was accounted for based on geographic data using the Swedish Municipalities Classification: Metropolitan area (reference group), larger and commuting cities and rural areas.³¹ Need of elderly care was stratified into “no need” (reference group) and “need of elderly care”. Education level was classified as primary, secondary, or higher education (university-level; reference group). Annual disposable income was categorized into

WHO clinical progression scale	Adapted for nordic registry data
 0. No infection: No registered laboratory-verified positive tests	 0. No infection: No registered laboratory-verified positive tests
 1. Ambulatory mild disease: Asymptomatic; positive test	 1. Ambulatory mild disease: Positive test, no contact with outpatient or inpatient clinic
 2. Ambulatory mild disease Symptomatic; independent	 2. Ambulatory mild disease Symptomatic; assistance needed. Contact with outpatient clinic <i>or</i> hospitalised 1 day
 3. Ambulatory mild disease Symptomatic; assistance needed	
 4. Hospitalised: Moderate disease Hospitalised; No oxygen	 3. Hospitalised: Moderate disease Hospitalised; 2-5 days
 5. Hospitalised: Moderate disease Hospitalised; oxygen by mask or nasal prongs	 4. Hospitalised: Moderate disease Hospitalised; > 5 days
 6. Hospitalised: severe diseases Hospitalised; oxygen by NIV/HFO	 5. Hospitalised: severe diseases Hospitalised; oxygen by NIV/HFO <i>or</i> dialysis <i>or</i> intensive care
 7. Hospitalised: severe diseases Mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	 6. Hospitalised: severe diseases Mechanical ventilation, mild <i>or</i> moderate ARDS
 8. Hospitalised: severe diseases Mechanical ventilation, $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ <i>or</i> vasopressors	 7. Hospitalised: severe diseases Mechanical ventilation, severe ARDS
 9. Hospitalised: severe diseases Mechanical ventilation, $pO_2/FiO_2 < 150$ <i>and</i> vasopressors, dialysis, or ECMO	 8. Hospitalised: severe diseases Extracorporeal membrane oxygenation (ECMO) / Extracorporeal life support (ECLS)
 10. Dead Death due to infection	 9. Dead Death due to infection

Figure 2 Translation of the WHO COVID-19 Clinical Progression Scale. Map of the WHO COVID-19 Clinical Progression Scale disease severity categories (left) compared to the novel translated categories formatted for registry data (right). Figure made with Biorender.

quartiles: highest (reference group), high, low and lowest. Finally, region of birth was categorized as born in Sweden (reference), Europe, Asia/Oceania, Africa, North America, South America.

Statistical Analysis

A descriptive analysis was performed for all co-variates for the whole study group, and for each disease severity group to identify factors associated with increasing severity.

To validate the Disease Severity Index (DSI), the all-cause mortality hazard ratio (HR) and 95% confidence intervals (CI) were calculated for survivors following the first month, 31–120 days (90-day mortality), using Cox proportional

hazard regression. The non-infected category was used as the reference. Potential confounders were included in the multivariable model including sex and region of birth, and time-varying covariates (vaccination, living in an elderly care home, wCCI, age, income and education) (updated yearly). Time-varying covariates were handled in a counting process-style, where each individual contributed with observation time both as infected and non-infected, reported in total numbers and person years. Robust standard errors are adjusted for dependencies in repeated observation periods. Covariates were updated annually at the start of the randomized index date for non-infected and one month before the infection date for each new registered infection. Study participants were censored at registered death. Kaplan–Meier curves were used to detect deviations from the proportional hazard assumption ([Supplementary Figure 2](#)). The analysis was stratified by pandemic waves, defined by peaks of registered positive SARS-CoV-2 tests and burden of ICU ([Supplementary Figure 1A](#) and [B](#) and [Supplementary Table 2](#)) considering evolving viral strains, guideline changes and health-care saturation. The analyses were performed using R version 4.3.3.

Results

Characteristics of the Swedish Population Included in the Study

This study included 8,245,474 unique individuals aged 18 or older from the entire Swedish population during the study period ([Figure 1](#) and [Table 1](#)). About 1,981,946 adults tested positive for SARS-CoV-2 between January 1st, 2020, and

Table 1 Characteristics of the Study Cohort: Descriptive Data at Time of Inclusion (January 1st, 2020)

Variable	Number	%
Age Groups		
18-49	4,268,882	51.8%
50-64	1,166,504	22.6%
65-79	1,544,331	18.7%
80+	565,757	6.9%
Sex		
Male	3,797,048	49.9%
Female	3,837,954	50.1%
Municipality type		
Metropolitan area	3,009,992	36.5%
Larger and commuting cities	3,318,621	40.3%
Rural area	1,916,861	23.3%
Elderly care		
Yes	87,162	1.1%
No	8,158,312	98.9%
Education		
Higher Education	3,112,471	37.8%
Secondary Education	3,549,607	43.1%
Primary Education	1,583,396	19.2%

(Continued)

Table 1 (Continued).

Variable	Number	%
Disposable income		
Highest	2,087,918	25.3%
Higher	2,040,103	24.7%
Low	2,040,103	25.0%
Lowest	2,056,475	24.9%
Region of birth		
Asia/Oceania	713,460	8.7%
Africa	190,152	2.3%
South America	70,107	0.9%
North America	35,037	0.4%
Europe	696,426	8.4%
Sweden	6,540,292	79.3%
Number of vaccinations per individual (total over whole study period)		
0	1,014,198	12.3%
1	1,694,301	20.5%
2	3,801,539	46.1%
3	1,717,253	20.8%
4+	18,183	0.2%
Number of laboratory verified SARS-CoV-2 positive tests per individual		
1	1,876,721	94.7%
2	105,000	5.3%
3	225	<0.1%

July 27, 2022 ([Figure 1](#)). Together, they contributed with 15,355 767 person years of observation time ([Tables 2](#) and [3](#)). During the observation period, 7,231,276 (87.7%) individuals were vaccinated with at least one vaccine dose, and more than 5% had a SARS-CoV-2 reinfection ([Table 1](#)). The characteristics of COVID-19 patients who died due to COVID-19 within the first month are shown in [Supplementary Table 3](#). Previous SARS-CoV-2 infection did not seem to have a protective effect of higher disease severity post re-infection ([Supplementary Table 4](#)).

COVID-19 Disease Severity Index for Registry-Based Data Format

No SARS-CoV-2 Infection – Severity Index Category 0

The WHO outcome “uninfected” (score 0) was defined as DSI category 0 including individuals without a registered laboratory-verified positive test for SARS-CoV-2 within 365 days post index date (n = 8,225,498) ([Table 2](#)). The majority of individuals were aged 18 to 64 years and had no recorded comorbidities ([Tables 2](#) and [3](#)).

Table 2 Main Results of the Disease Severity Index for the Whole Study Period with Information on All Variables for All Disease Severity Categories in Numbers (N) and % (Only First Infection and Worst Outcome, Non-Infected Persons Not included). Groups with Less Than 3 Individuals Were Presented as <3. Region of Birth Was Combined Into Three Categories Because of Few Individuals in Subgroups. Disease Severity Index Group 8 with Weighted Charlson Comorbidity Index Category 5+ is Included in the Weighted Charlson Comorbidity Index Group 3–4 Since There Were Too Few Individuals in One of the Groups. Proportions in % Cannot Be Presented for All Subgroups in Disease Severity Index Group 8, Due to Few Individuals and Risk of Identification

Disease Severity Category	0: No Laboratory Verified Infection	1: No Health Care Contact	2: Outpatient or Inpatient 1 Day	3: Inpatient 2–5 Days	4: Inpatient > 5 Days	5: Inpatient + Organ Support/ICU	6: Mechanical Ventilation, Mild or Moderate ARDS	7: Mechanical Ventilation, Severe ARDS	8: ECMO or ECLS	9: Death
Individuals, N, (%)	N = 8225498	N = 1867253	N = 42066	N = 26988	N = 25301	N = 9648	N = 2356	N = 1955	N = 65	N = 13110
Weighted CCI groups										
0	5656208(68.8%)	1431345(76.7%)	25658 (61.0%)	12726 (47.2%)	7164 (28.3%)	4430 (45.9%)	1220 (51.8%)	1019 (52.1%)	41 (63.1%)	1532 (11.7%)
1–2	1506607 (18.3%)	262 038 (14.0%)	8535 (20.3%)	6737 (25.0%)	7060 (27.9%)	2476 (25.7%)	657 (27.9%)	549 (28.1%)	15 (23.1%)	3924 (29.9%)
3–4	363 373 (4.4%)	37547 (2.0%)	2252 (5.4%)	2982 (11.0%)	4619 (18.3%)	1111 (11.5%)	213 (9.0%)	176 (9.0%)	3 (4.6%)	3444 (26.3%)
5+	699 310 (8.5%)	136 323 (7.3%)	5621 (13.4%)	4543 (16.8%)	6458 (25.5%)	1631 (16.9%)	266 (11.3%)	211 (10.8%)	6 (9.2%)	4210 (32.1%)
Sex										
Women	4123772 (50.1%)	1009907(54.1%)	24214 (57.6%)	12217 (45.3%)	11476 (45.4%)	3420 (35.4%)	702 (29.8%)	542 (27.7%)	16 (24.6%)	5951 (45.4%)
Men	4101726 (49.9%)	857 346 (45.9%)	17852 (42.4%)	14771 (54.7%)	13825 (54.6%)	6228 (64.6%)	1654 (70.2%)	1413 (72.3%)	49 (75.4%)	7159 (54.6%)
Age										
18–49	4055985 (49.3%)	1264743 (67.7%)	22447 (53.4%)	7638 (28.3%)	2585 (10.2%)	1940 (20.1%)	460 (19.5%)	289 (14.8%)	33 (50.8%)	96 (0.7%)
50–64	1891435 (23.0%)	441 752 (23.7%)	11708 (27.8%)	7664 (28.4%)	4588 (18.1%)	3142 (32.6%)	856 (36.3%)	835 (42.7%)	29 (44.6%)	530 (4.0%)
65–79	1603926 (19.5%)	114 296 (6.1%)	5489 (13.0%)	6934 (25.7%)	8560 (33.8%)	3255 (33.7%)	929 (39.4%)	790 (40.4%)	3 (4.6%)	3274 (25.0%)
80+	674 152 (8.2%)	46462 (2.5%)	2422 (5.8%)	4752 (17.6%)	9568 (37.8%)	1311 (13.6%)	111 (4.7%)	41 (2.1%)	0 (0%)	9210 (70.3%)
Vaccination status										
Not vaccinated	1579386 (19.2%)	893 835 (47.9%)	30410 (72.3%)	19359 (71.7%)	17591 (69.5%)	7969 (82.6%)	2022 (85.8%)	1835 (93.9%)	62 (95.4%)	12292 (93.8%)
First dose within 3 months	654 316 (8.0%)	42168 (2.3%)	695 (1.7%)	481 (1.8%)	616 (2.4%)	149 (1.5%)	31 (1.3%)	20 (1.0%)	<3 (<4.5%)	358 (2.7%)
First dose plus 3 months	3097283 (37.7%)	618 066 (33.1%)	5026 (11.9%)	2061 (7.6%)	1859 (7.3%)	463 (4.8%)	108 (4.6%)	43 (2.2%)	<3 (<4.5%)	409 (3.1%)
Two or more vaccinations	2894513 (35.2%)	313 184 (16.8%)	5935 (14.1%)	5087 (18.8%)	5235 (20.7%)	1067 (11.1%)	195 (8.3%)	57 (2.9%)	<3 (<4.5%)	51 (0.4%)
Municipality type										
Larger and commuting cities	3312696 (40.3%)	746 345 (40.0%)	18523 (44.0%)	10731 (39.8%)	9027 (35.7%)	3874 (40.2%)	1046 (44.4%)	719 (36.8%)	18 (27.7%)	4797 (36.6%)
Metropolitan area	2997939 (36.4%)	739 097 (39.6%)	14370 (34.2%)	10535 (39.0%)	11696 (46.2%)	3803 (39.4%)	776 (32.9%)	890 (45.5%)	38 (58.5%)	5439 (41.5%)
Rural area	1914863 (23.3%)	381 811 (20.4%)	9173 (21.8%)	5722 (21.2%)	4578 (18.1%)	1971 (20.4%)	534 (22.7%)	346 (17.7%)	9 (13.8%)	2874 (21.9%)

(Continued)

Table 2 (Continued).

Disease Severity Category	0: No Laboratory Verified Infection	1: No Health Care Contact	2: Outpatient or Inpatient 1 Day	3: Inpatient 2–5 Days	4: Inpatient > 5 Days	5: Inpatient + Organ Support/ICU	6: Mechanical Ventilation, Mild or Moderate ARDS	7: Mechanical Ventilation, Severe ARDS	8: ECMO or ECLS	9: Death
Individuals, N, (%)	N = 8225498	N = 1867253	N = 42066	N = 26988	N = 25301	N = 9648	N = 2356	N = 1955	N = 65	N = 13110
Elderly Care										
No	8109438 (98.6%)	1838317 (98.5%)	41454 (98.5%)	26043 (96.5%)	23881 (94.4%)	9434 (97.8%)	2341 (99.4%)	1950 (99.7%)	65 (100%)	9749 (74.4%)
Yes	116 060 (1.4%)	28936 (1.5%)	612 (1.5%)	945 (3.5%)	1420 (5.6%)	214 (2.2%)	15 (0.6%)	5 (0.3%)	0 (0%)	3361 (25.6%)
Education										
Higher Education	3114826 (37.9%)	795 585 (42.6%)	15852 (37.7%)	8053 (29.8%)	6177 (24.4%)	2559 (26.5%)	610 (25.9%)	531 (27.2%)	23 (35.4%)	2243 (17.1%)
Secondary Education	3545705 (43.1%)	808 771 (43.3%)	18139 (43.1%)	11641 (43.1%)	10630 (42.0%)	4280 (44.4%)	1060 (45.0%)	891 (45.6%)	31 (47.7%)	4973 (37.9%)
Primary Education	1564967 (19.0%)	262 897 (14.1%)	8075 (19.2%)	7294 (27.0%)	8494 (33.6%)	2809 (29.1%)	686 (29.1%)	533 (27.3%)	11 (16.9%)	5894 (45.0%)
Disposable income										
Highest	2463668 (30.0%)	574 236 (30.8%)	10605 (25.2%)	6147 (22.8%)	4300 (17.0%)	2122 (22.0%)	498 (21.1%)	481 (24.6%)	13 (20.0%)	1292 (9.9%)
High	2108113 (25.6%)	555 049 (29.7%)	10378 (24.7%)	5537 (20.5%)	4081 (16.1%)	2022 (21.0%)	510 (21.6%)	438 (22.4%)	13 (20.0%)	1242 (9.5%)
Low	1941615 (23.6%)	451 639 (24.2%)	10601 (25.2%)	6930 (25.7%)	7362 (29.1%)	2476 (25.7%)	572 (24.3%)	470 (24.0%)	19 (29.2%)	3878 (29.6%)
Lowest	1712102 (20.8%)	286 329 (15.3%)	10482 (24.9%)	8374 (31.0%)	9558 (37.8%)	3028 (31.4%)	776 (32.9%)	566 (29.0%)	20 (30.8%)	6698 (51.1%)
Region of birth										
Sweden	6522659 (79.3%)	1464872 (78.5%)	27308 (64.9%)	17893 (66.3%)	18336 (72.5%)	6106 (63.3%)	1521 (64.6%)	1131 (57.9%)	25 (38.5%)	10788 (82.3%)
Europe except Sweden	695 326 (8.5%)	147 836 (7.9%)	4503 (10.7%)	3140 (11.6%)	3392 (13.4%)	1349 (14.0%)	286 (12.1%)	283 (14.5%)	7 (10.8%)	1621 (12.4%)
Non-European	1007513 (12.2%)	254 545 (13.6%)	10255 (24.4%)	5955 (22.1%)	3573 (14.1%)	2193 (22.7%)	549 (23.3%)	541 (27.7%)	33 (50.8%)	701 (5.3%)

Abbreviations: CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; ARDS, Acute Respiratory Distress Syndrome; ECMO, Extracorporeal Membrane Oxygenation; ECLS, Extra Corporeal Life Support.

Table 3 Overview of Distribution of Person Years for the Population for the Whole Study Period by Disease Severity Index Groups (Total Observation Time)

	0: No Laboratory Verified Infection	1: No Health Care Contact	2: Outpatient Contact Only or Inpatient Visits 1 Day	3: Inpatient 2–5 Days	4: Inpatient > 5 Days	5: Inpatient + Organ Support/ ICU	6: Mechanical Pulmonary Ventilation Mild/Moderate ARDS	7: Mechanical Pulmonary Ventilation Severe ARDS	8: ECMO or ECLS	9: Death
	Person Years = 13987264	Person Years = 1296858	Person Years = 27529	Person Years = 17810	Person Years = 16843	Person Years = 6233	Person Years = 1606	Person Years = 1183	Person Years = 32	Person Years = 409
Weighted CCI groups										
0	10 554 166 (70.05%)	1 103 373 (77.45%)	21 453 (64.30%)	11 090 (52.24%)	6 132 (32.73%)	4 020 (50.45%)	1 049 (55.12%)	806 (55.81%)	33 (70.22%)	57 (13.47%)
1–2	2 734 528 (18.15%)	196 401 (13.79%)	6 496 (19.47%)	5 199 (24.49%)	5 350 (28.56%)	2 025 (25.41%)	534 (28.05%)	385 (26.66%)	9 (19.66%)	131 (30.82%)
3–4	620 906 (4.12%)	25 546 (1.79%)	1 429 (4.28%)	1 948 (9.17%)	3 138 (16.75%)	806 (10.12%)	145 (7.63%)	116 (8.00%)	1 (2.36%)	109 (25.70%)
5+	1 156 781 (7.68%)	99 322 (6.97%)	3 989 (11.95%)	2 994 (14.10%)	4 116 (21.97%)	1 117 (14.02%)	175 (9.20%)	138 (9.54%)	4 (7.76%)	127 (30.01%)
Sex										
Women	7 515 071 (49.88%)	760 775 (53.40%)	19 303 (57.85%)	9 558 (45.02%)	8 535 (45.55%)	2 788 (34.99%)	571 (30.00%)	407 (28.19%)	14 (31.07%)	190 (44.88%)
Men	7 551 309 (50.12%)	663 867 (46.60%)	14 063 (42.15%)	11 672 (54.98%)	10 202 (54.45%)	5 180 (65.01%)	1 332 (70.00%)	1 037 (71.81%)	32 (68.93%)	234 (55.12%)
Age category										
18–49	7 391 568 (49.06%)	976 472 (68.54%)	18 322 (54.91%)	6 576 (30.98%)	2 258 (12.05%)	1 743 (21.88%)	409 (21.48%)	255 (17.69%)	26 (55.20%)	3 (0.78%)
50–64	3 504 103 (23.26%)	336 682 (23.63%)	9 882 (29.62%)	6 773 (31.90%)	4 000 (21.35%)	2 866 (35.96%)	749 (39.34%)	667 (46.19%)	19 (41.83%)	21 (5.05%)
65–79	3 075 482 (20.41%)	84 024 (5.90%)	3 874 (11.61%)	5 169 (24.35%)	6 408 (34.20%)	2 578 (32.35%)	686 (36.03%)	501 (34.69%)	1 (2.97%)	116 (27.40%)
80+	1 095 227 (7.27%)	27 464 (1.93%)	1 287 (3.86%)	2 712 (12.77%)	6 071 (32.40%)	782 (9.81%)	60 (3.15%)	21 (1.43%)	0 (0.00%)	283 (66.78%)
Vaccination status										
Not vaccinated	10 902 149 (72.36%)	909 280 (63.83%)	27 952 (83.77%)	17 926 (84.44%)	15 496 (82.70%)	7 191 (90.25%)	1 766 (92.78%)	1 390 (96.22%)	46 (98.94%)	399 (94.02%)
First dose within 3 months	1 161 162 (7.71%)	33 222 (2.33%)	544 (1.63%)	394 (1.86%)	490 (2.61%)	114 (1.43%)	22 (1.14%)	13 (0.92%)	<1 (0.01%)	11 (2.50%)
First dose > 3 months after	1 971 419 (13.08%)	332 138 (23.31%)	2 547 (7.63%)	1 019 (4.80%)	897 (4.79%)	227 (2.85%)	44 (2.31%)	15 (1.01%)	<1 (0.02%)	13 (3.10%)
Two or more vaccinations	1 031 650 (6.85%)	150 001 (10.53%)	2 323 (6.96%)	1 891 (8.91%)	1 855 (9.90%)	436 (5.48%)	72 (3.78%)	27 (1.86%)	<1 (1.03%)	2 (0.37%)
Municipality type										
Metropolitan area	5 448 884 (36.17%)	576 259 (40.45%)	11 600 (34.77%)	8 694 (40.95%)	8 847 (47.22%)	3 181 (39.92%)	622 (32.69%)	663 (45.93%)	29 (63.25%)	174 (40.93%)
Larger and commuting cities	6 074 516 (40.32%)	563 108 (39.53%)	14 757 (44.23%)	8 372 (39.43%)	6 683 (35.67%)	3 217 (40.38%)	868 (45.58%)	537 (37.16%)	11 (23.06%)	157 (36.92%)
Rural area	3 542 980 (23.52%)	285 274 (20.02%)	7 009 (21.01%)	4 164 (19.61%)	3 207 (17.12%)	1 570 (19.70%)	414 (21.74%)	244 (16.91%)	6 (13.69%)	94 (22.15%)

(Continued)

Table 3 (Continued).

	0: No Laboratory Verified Infection	1: No Health Care Contact	2: Outpatient Contact Only or Inpatient Visits 1 Day	3: Inpatient 2–5 Days	4: Inpatient > 5 Days	5: Inpatient + Organ Support/ ICU	6: Mechanical Pulmonary Ventilation Mild/Moderate ARDS	7: Mechanical Pulmonary Ventilation Severe ARDS	8: ECMO or ECLS	9: Death
	Person Years = 13987264	Person Years = 1296858	Person Years = 27529	Person Years = 17810	Person Years = 16843	Person Years = 6233	Person Years = 1606	Person Years = 1183	Person Years = 32	Person Years = 409
Elderly Care										
No	14 932 752 (99.11%)	1 407 744 (98.81%)	33 029 (98.99%)	20 687 (97.44%)	17 907 (95.57%)	7 848 (98.49%)	1 896 (99.59%)	1 442 (99.84%)	47 (100.00%)	309 (72.93%)
Yes	133 628 (0.89%)	16 898 (1.19%)	337 (1.01%)	544 (2.56%)	829 (4.43%)	120 (1.51%)	8 (0.41%)	2 (0.16%)	0 (0.00%)	115 (27.07%)
Education										
Higher Education	5 757 307 (38.21%)	601 619 (42.23%)	13 016 (39.01%)	6 610 (31.14%)	4 807 (25.65%)	2 200 (27.60%)	509 (26.73%)	390 (26.99%)	15 (32.38%)	75 (17.76%)
Secondary Education	2 730 336 (18.12%)	197 866 (13.89%)	5 939 (17.80%)	5 387 (25.37%)	6 041 (32.24%)	2 192 (27.51%)	538 (28.27%)	392 (27.12%)	8 (16.96%)	188 (44.31%)
Primary Education	6 578 737 (43.67%)	625 157 (43.88%)	14 412 (43.19%)	9 233 (43.49%)	7 889 (42.10%)	3 576 (44.88%)	857 (45.00%)	663 (45.89%)	24 (50.66%)	161 (37.92%)
Disposable income										
Highest	4 177 512 (27.73%)	439 088 (30.82%)	8 668 (25.98%)	5 073 (23.90%)	3 400 (18.15%)	1 872 (23.49%)	426 (22.36%)	370 (25.63%)	8 (18.22%)	46 (10.77%)
High	3 756 092 (24.93%)	423 456 (29.72%)	8 440 (25.30%)	4 549 (21.43%)	3 135 (16.73%)	1 749 (21.94%)	419 (22.01%)	327 (22.62%)	12 (24.93%)	43 (10.10%)
Low	3 646 056 (24.20%)	342 852 (24.07%)	8 286 (24.83%)	5 255 (24.75%)	5 254 (28.04%)	1 951 (24.49%)	451 (23.70%)	348 (24.09%)	11 (23.42%)	126 (29.64%)
Lowest	3 486 721 (23.14%)	219 246 (15.39%)	7 972 (23.89%)	6 353 (29.92%)	6 948 (37.08%)	2 396 (30.08%)	608 (31.93%)	399 (27.66%)	16 (33.44%)	210 (49.48%)
Region of birth										
Africa	350 670 (2.33%)	32 240 (2.26%)	1 266 (3.79%)	836 (3.94%)	446 (2.38%)	279 (3.51%)	89 (4.65%)	66 (4.54%)	3 (5.54%)	4 (0.89%)
Asia/Oceania	1 285 403 (8.53%)	150 828 (10.59%)	6 711 (20.11%)	4 041 (19.03%)	2 356 (12.58%)	1 502 (18.85%)	351 (18.42%)	308 (21.30%)	16 (33.55%)	19 (4.60%)
Europe	1 285 986 (8.54%)	112 915 (7.93%)	3 628 (10.87%)	2 507 (11.81%)	2 565 (13.69%)	1 099 (13.79%)	235 (12.34%)	204 (14.12%)	7 (14.40%)	52 (12.34%)
North America	64 855 (0.43%)	5 964 (0.42%)	135 (0.40%)	108 (0.51%)	53 (0.28%)	36 (0.45%)	7 (0.35%)	6 (0.40%)	1 (2.57%)	1 (0.19%)
South America	127 165 (0.84%)	14 700 (1.03%)	528 (1.58%)	352 (1.66%)	287 (1.53%)	175 (2.20%)	41 (2.13%)	24 (1.68%)	3 (6.97%)	3 (0.60%)
Sweden	11 952 301 (79.33%)	1 107 994 (77.77%)	21 098 (63.23%)	13 387 (63.06%)	13 030 (69.54%)	4 877 (61.20%)	1 182 (62.11%)	837 (57.96%)	17 (36.98%)	345 (81.38%)

Abbreviations: CCI, Charlson Comorbidity Index; ICU, Intensive Care Unit; ARDS, Acute Respiratory Distress Syndrome; ECMO, Extracorporeal Membrane Oxygenation; ECLS, Extra Corporeal Life Support.

SARS-CoV-2 Infection – Severity Index Categories 1–9

Individuals with a registered laboratory-verified positive SARS-CoV-2 test were categorized into severity index categories 1–9 based on the WHO Clinical Progression Scale, which has 10 severity stratifications (Figure 2). The main inclusion criteria was a laboratory-verified positive SARS-CoV-2 test in SmiNet.

COVID-19 Severity Index Categories 1–2: Ambulatory Mild Disease

The WHO category “ambulatory mild COVID-19” is subdivided into three groups: “asymptomatic” (score 1); “symptomatic: independent” (score 2); or “symptomatic: assistance needed” (score 3).

These categories are not translatable to nationwide registry data, since symptoms are not consistently recorded for each patient. In some Nordic countries (eg Denmark) the registries do not differentiate between outpatient and inpatient visits, consequently it is difficult to distinguish between outpatient visits and a short inpatient stays. To enable cross-country comparison, we created two sub-categories for the WHO Ambulatory Mild Disease that were defined as DSI 1: “no contact with outpatient or inpatient clinics” ($n = 1,867,253$); and 2: “contact with outpatient clinic and/or hospitalized maximum one day due to COVID-19” ($n = 42,066$) (Figure 2 and Table 2). Individuals in DSI 1 were generally younger and had fewer comorbidities compared to the population (Table 2 and Table 3). In contrast to DSI 1, individuals in DSI 2 had higher wCCI than the reference population, with nearly double the proportion of individuals with wCCI 5 or above (7.3% vs 13.4%, respectively) (Table 2).

COVID-19 Severity Index Categories 3–4: Hospitalized; Moderate Disease

The WHO category “Hospitalized, moderate disease” is subdivided into the categories: “hospitalized, no oxygen” (score 4) and “hospitalized with need of atmospheric pressure oxygen by mask or nasal prongs” (score 5) (Figure 2).

The fourth WHO category “hospitalized, no oxygen” can be translated to hospitalization. However, the procedure code for supplemental oxygen (DG015) is rarely registered. To refine severity measures, the length of hospital stay was considered, with hospitalization 2–5 days (DSI 3: $n = 26,988$) or >5 days (DSI 4: $n = 25,301$) (Figure 2 and Table 2).

Key differences in characteristics of patients in DSI 3 vs DSI 4 were higher age and comorbidity burden (Table 2 and Table 3). The proportion of patients aged 80 years or older was 17.6% in DSI 3 versus 37.8% in DSI 4. Additionally, 16.8% of DSI 3 patients had a wCCI of 5 or more, compared to 25.5% in DSI 4 (Table 2).

COVID-19 Severity Index Categories 5–8: Hospitalized; Severe Diseases

The WHO category “Hospitalized, severe diseases” is subdivided into four categories: “Hospitalized; oxygen by non-invasive ventilation (NIV) or high-flow oxygen (HFO)” (score 6); “Hospitalized, mechanical ventilation (MV) $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ ” (score 7); “Hospitalized, MV $pO_2/FiO_2 < 150$ or $SpO_2/FiO_2 < 200$ or vasopressors” (score 8) and “Hospitalized, MV, $pO_2/FiO_2 < 150$ and vasopressors, dialysis or extracorporeal membrane oxygenation (ECMO)” (score 9) (Figure 2).

The category “Hospitalized, oxygen by NIV/HFO” was translated into DSI category 5 (Figure 2), including patients who received NIV/HFO (medical procedure codes shown in Supplementary Table 1), and COVID-19 patients requiring intensive care (without MV) or dialysis ($n = 9648$) (Table 2). The WHO scores 7–9 could not be translated due to low quality of $pO_2/FiO_2/SpO_2$ data in SIR. Instead, DSI 6 was defined as COVID-19 patients requiring MV with mild or moderate Acute Respiratory Distress Syndrome (ARDS) (DSI 6: $n = 2356$) (Table 2). DSI 7 was defined as COVID-19 patients needing MV with severe ARDS (DSI 7: $n = 1955$) (Table 2). DSI 8 was reserved for patients requiring ECMO or extracorporeal life support (ECLS), a treatment only given to the most severe COVID-19 cases ($n = 65$) (Table 2). Age and comorbidity decreased from DSI categories 4 to 8 (Table 2 and Table 3). The proportion of individuals that were 80 years or older was 37.8% in DSI 4, which decreased to 13.6% in DSI 5, 4.7% in DSI 6, 2.1% in DSI 7 and 0% in DSI 8 (Table 2).

COVID-19 Index Severity Category 9: Death Due to COVID-19

The WHO outcome “Dead due to COVID-19” (score 10) was translated into COVID-19 patients that died due to COVID-19 (DSI 9: $n = 13,110$) (Figure 2 and Table 2). Of these, 54.6% were men (Table 2).

The majority (93.8%) were unvaccinated, older, had the highest comorbidity burden, and lived in an elderly care home (25.6%) (Table 2). About 40.8% of the fatal cases had no contact with out-/or-inpatient clinics prior to their death (Supplementary Table 3). The majority of the remaining fatal cases were hospitalized but did not receive advanced life support (MV or ECMO) (Supplementary Table 3).

Risk of All-Cause 90-Day Mortality for COVID-19 Survivors Stratified by Initial Severity

The all-cause 90-day mortality was analyzed stratified by the initial severity in COVID-19 survivors (DSI1-8) compared to the population (DSI0) (Figure 3; Supplementary Figure 2 and Supplementary Table 5). COVID-19 survivors had a higher risk of death, even in the minimal severity group with no registered health care due to COVID-19 (DSI 1) HR 1.18 (95% CI 1.13–1.22) (Figure 3). For patients hospitalized >5 days (DSI 4) the HR was 5.83 (95% CI 5.5–6.17) (Figure 3). The highest all-cause mortality risk was identified in COVID-19 cases requiring ECMO/ECLS (DSI 8) (HR 593.54 (95% CI 317.77–1108.65) (Figure 3).

In the unadjusted model, DSI-group 4 had a higher all-cause mortality risk than DSI-group 5, HR 28.25 (95% CI 26.83–29.75) compared to HR 18.62 (95% CI 16.83–20.61) (Supplementary Table 5). However, when the analysis was adjusted for disease severity index, wCCI, sex, age and elderly care, the risk for all-cause mortality increased with each DSI-category (Figure 3 and Supplementary Table 5). Overall, the trend in 90-day all-cause mortality consistently increased with the severity of COVID-19, reflecting greater risk across all pandemic phases (Figure 3; Supplementary Figures 2 and 3A–D).

Effect of Socio-Economic and Demographic Factors

Socio-economic and demographic factors; lower income and education level, and living in rural areas, were associated with higher hazard ratio of all-cause mortality the whole study period, while being born outside of Sweden was not (Figure 3). Among those who died within 30 days post COVID-19 date (DSI9), 80.7% were in the two lowest disposable income groups (lowest: 51.1%, low: 29.6%), and 45% had the lowest education level (primary education), compared to 37.9% with secondary education and 17.1% with higher education (Table 2). The group with primary education represented 19% of the whole study cohort (Table 1), and constituted 27–33.6% of the higher DSI-groups (3–7) in need of hospitalization or organ support, and 16.9% in DSI group 8 (ECMO or ECLS) (Table 2).

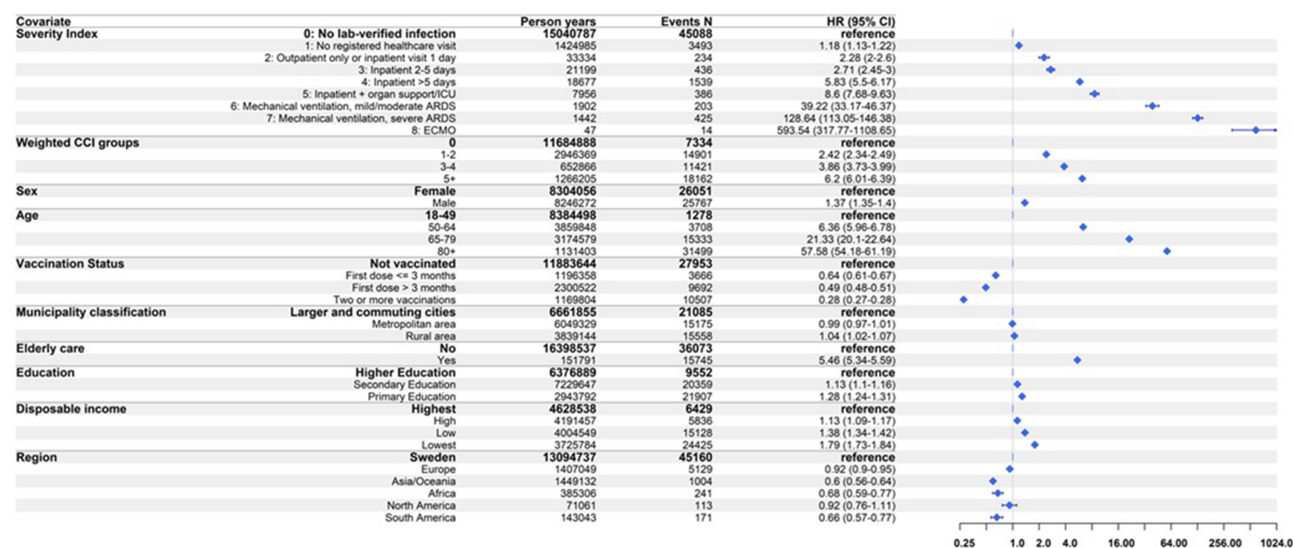


Figure 3 Forest plot with hazard ratios for all-cause mortality. To validate the Disease Severity Index (DSI), the adjusted all-cause mortality hazard ratio (HR) and 95% confidence intervals (CI) were calculated following the first month, 31–120 days post COVID-19 date or index date, for disease severity groups 0–8 (90-day mortality), using Cox proportional hazard regression.

About 36.5% of the whole study cohort lived in a metropolitan area (Table 1) and they contributed with 46.2% in DSI-group 4 (hospitalized >5 days), 45.5% in DSI-group 7 (MV and severe ARDS), 58.5% in DSI-group 8 (ECMO or ECLS) and 41.5% in DSI-group 9 (death due to COVID-19) (Table 2). However, living in a metropolitan area was not associated with higher hazard ratio of all-cause mortality the whole study period in the adjusted analysis (HR 0.99 (95% CI 0.97–1.01)), which living in a rural area was (HR 1.04 (95% CI 1.02–1.07)) (Figure 3).

Discussion

A severity index for viral disease was created using Nordic registry data, adapted from the WHO Clinical Progression Scale. A clinically relevant COVID-19 DSI adapted for large register studies is important for the comparison of epidemiological studies within the Nordics as well as globally. It is a novel tool for register-based research, which can help standardize definitions and analyses in this extensive and rapidly developing field of research. Standardized definitions and analysis in register-based infectious disease research has the potential to better guide public health policies as well as clinical guidelines and health-care priorities.

Severe and fatal COVID-19 patients were generally older, male, unvaccinated with a higher comorbidity burden. COVID-19 survivors that did not require specialized health care still had a two-fold increased risk of all-cause mortality compared to the population, despite adjusting for age, elderly care, comorbidities and other covariates. The risk of mortality increased with severity consistent throughout the pandemic periods, after adjusting for age, sex, comorbidities, among others. The mortality risk scores conform to other studies investigating mortality post-COVID-19.^{32–35} By adapting the WHO clinical progression scale to registry data, the tool was validated in a national dataset.

Limited access to clinical data and limited information on treatment during hospitalization in the Swedish health-care registries, and across the Nordic countries, is a limitation for applying clinical severity classifications to registry-based studies.¹⁸ The main challenge in creating the DSI was the lack of individual-reported data in health-care registries, complicating the direct translation of the WHO's lower severity categories to registry data.¹⁶ To address this, we stratified participants based on their contact with outpatient or inpatient clinics.

Furthermore, Nordic registry formats differ, causing challenges in identifying outpatient visits (Denmark lacks a specific outpatient registry). This highlights the importance of standardized health data infrastructure beyond national borders. To enable comparative Nordic and international studies, we treated hospitalization for up to one day as equivalent to outpatient clinic contact. The category “hospitalized with oxygen by mask or nasal prongs” (WHO score 5) was dependent on complete reporting of oxygen treatment procedure codes (DG015) to the inpatient registry. According to NBHW, and clinical experience, these procedure codes are not reported adequately. Instead, hospitalization length was included to create two severity categories for hospitalized COVID-19 patients that did not need NIV/HFO, dialysis, intensive care, MV or ECMO/ECLS. Severe COVID-19 patients who were treated in ICU during the early pandemic were more likely to be managed with NIV/HFO in infectious disease clinics during later phases, due to limited ICU resources and updated guidelines. To ensure comparability of outcomes across the pandemic, COVID-19 patients who required intensive care (without MV) or NIV/HFO and/or dialysis but at a non-ICU ward, were stratified into the same category. The Swedish Intensive Care Registry data for pO₂/FiO₂ and SpO₂/FiO₂ is of low quality (personal communication from SIR staff). In addition, vasopressor administration is not present in the Inpatient Registry, therefore the WHO categories including pO₂/FiO₂ or SpO₂/FiO₂ and vasopressors (WHO score 7–9) were converted according to MV and ARDS severity.

Lower education, lower disposable income and rural living were factors associated with higher hazard ratios for all-cause mortality post-infection. These findings align with previous research on COVID-19's inequitable impact in Sweden, during the early pandemic.³⁶ In contrast to previous studies on the early phases of the pandemic,³⁷ individuals born outside of Sweden did not have higher risk of dying (all-cause mortality) post COVID-19 compared to individuals born in Sweden. However, differences in pandemic phases and mortality in the first 30 days should be considered for fair comparison.

Our study has several strengths. All adults with laboratory-verified positive SARS-CoV-2 tests are included, minimizing selection bias. The study includes the full spectrum of COVID-19, from mild to fatal cases, unlike single or multi-center studies focused on hospitalized patients. This allows identification of individuals with minimal disease

severity. Furthermore, all adults in the Swedish population are included, which provides baseline characteristics in relation to COVID-19. Individuals with a previous positive SARS-CoV-2 test are included in the population after a one-year quarantine period. This reflects reality and minimizes selection bias, where otherwise only the healthiest and individuals not tested for COVID-19 would be included as reference population. Historical health-care data for all causes of contacts, allows for assessing the combined comorbidity burden in outpatient/inpatient settings and update it throughout the study. Furthermore, Statistics Sweden provides annually updated socio-economic and demographic data, ensuring the population demographics are valid and not affected by recall bias. Finally, the registry data is largely consistent across the Nordic countries,¹⁸ with minor differences in how and when data is reported. For example, Denmark has national registries for laboratory results and treatment during hospitalization not available in Sweden. However, in the Danish dataset, it is not always possible to differ between an outpatient contact in a specialized clinic and a short hospital stay, something we considered when designing the DSI. Nordic health registries use the international nomenclature for diagnoses and procedures (ICD and medical procedure codes), and the registration of all-cause mortality is mandatory and follows similar procedures. This makes all-cause mortality data more reliable for evaluating COVID-19's impact, as cause-specific deaths can be influenced by variations in testing and cause of death reporting.³⁸ Therefore, our DSI categories can be applied to COVID-19 in the Nordics and could potentially also be applied in other countries with similar standardized data formats, based on ICD and international procedure codes.

The DSI also has the potential of being validated for other viral pathogens reported in health registries, such as Respiratory Syncytial (RS-) virus, influenza, Puumala virus and Mpox, allowing nationwide comparisons of complication risk by DSI stratified by outbreak periods. Also for registered bacterial infections causing similar symptoms and outcomes as COVID-19, with the need for similar interventions and care, the DSI could be adapted and evaluated. The DSI can be used retrospectively, as in this study, but it also has the potential of being used in real-time surveillance or predictive modeling if real-time data is available, as, for example, in Denmark.

Additionally, the DSI could potentially support comparative effectiveness research-such as evaluating vaccine impact for different patient groups across severity levels, or guiding resource allocation across different outbreak periods and for different diseases.

There are limitations to our study. Register data relies on accurate registration from clinicians, which introduces the risk of misclassification bias. Negative SARS-CoV-2 tests were not registered in Sweden, and varying public testing availability introduced risk of misclassification and selection bias. There is a risk of residual confounding from unmeasured clinical variables, and possible severity misclassification due to reliance on administrative codes. According to personal communication from the Swedish NBHW, anatomical therapeutic codes (ATC) for pharmaceutical treatments are not adequately registered in the Patient Registry, and the representatives strongly advise against using these codes. Therefore, treatment with antivirals, immunomodulatory therapy or vasopressors is not available, and though there exists a procedure code for oxygen therapy at room atmospheric pressure, it is not registered adequately in the inpatient registry. Categorization based on these criteria would introduce errors.

The level of care during COVID-19 depends on the availability and accessibility of health-care resources, the quality and effectiveness of the treatment provided and the criteria and guidelines for admission and discharge. This could impact our DSI, since the availability of supportive treatment will determine if a patient may or may not receive hospital care and organ support. As a result, the patient may be classified in a lower disease severity category than their infection would have warranted. The limited register data available for COVID-19 patients who died due to COVID-19 without health-care contact (40.8%) constitutes another limitation. This made us create a specific severity group, DSI-group 9, to visualize that even patients without registered need of care and health interventions died due to COVID-19, and should therefore not be considered as patients with mild COVID-19.

There are also complexities related to vaccination timing and waning immunity post-infection or vaccination. We partly mitigated these limitations by considering time periods in our mortality study, however algorithms computing time from last vaccination or last infection could potentially be added in future models. We also acknowledge that the generalizability is affected as only the adult population is included in this study. Further studies are needed to develop and validate disease severity indexes specifically for children and the elderly, as care varies by age due to physiological differences, clinical guidelines, and health-care priorities.

Conclusions

We created a COVID-19 severity index with 9 groups with an aim to categorize disease severity in registry-based population studies with an international applicability. The disease severity index considers the increasing risk of all-cause mortality 30–120 days post-infection. We developed a comprehensive epidemiological tool that includes key health variables, such as comorbidities, age, and socio-economic status, to assess disease severity post-infection and stratified by periods. Previous studies define disease severity using various variables, or focusing on a single socioeconomic factor, such as education, income, or country of birth, and there are no previous adaptations made of the WHO COVID-19 Clinical Progression Scale for register-based studies.

With this DSI, we aim to present a common international ground for disease severity indexation in registry data. The DSI was created to provide clinicians and policymakers with a tool to interpret and compare results on infectious disease severity between studies to support risk assessment and better guide public health policies as well as clinical guidelines and health-care priorities. The DSI also has further potential of being validated for different pathogens and for real-time surveillance or predictive modeling.

Data Sharing Statement

Pseudonymized data used in this study can be made available upon request, if appropriate ethical and legal criteria are fulfilled by the potential receiver. Script for disease severity index and statistical analysis will be published online upon publication.

Ethical Approval

This study conformed to the Declaration of Helsinki and was approved in advance by the Swedish Ethical Review Authority (registration number 2020-02150, 20200512 with revisions 2020-02669, 20200603; 2020-034565, 20200702; 2020-06713; 20201230; 2021-00068, 20210129; 2021-00552, 20210223; 2021-01780, 20210409; 2021-04687, 20211203; 2022-03302-02, 20220706).

Acknowledgments

We thank Senior Physicians Ritva Kiiski Berggren, Camilla Brorsson and Matthias Schien, Helena Nyström MD PhD and Alicia Lind MD PhD for their valuable contributions. Their clinical experience in intensive care, infectious diseases, and their experience from working with the Swedish Intensive Care Register has been fundamental for this study.

This paper has been uploaded to The Lancet SSRN as a preprint: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5100756.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Swedish Research Council (grant number 2021-06536), Central and Base-ALF funding Region Västerbotten (grant numbers RV-1006715, RV-982300, RV-996166, RV-1010337), Heart-Lung Foundation (grant number 20220179), Kempe Foundation (grant number SMK21-0014).

Disclosure

Prof. Dr. Anders Hviid reports grants from Novo Nordisk Foundation, Lundbeck Foundation, and Independent Research Fund Denmark, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. World Health Organization. WHO global health estimates, the 10 top causes of death. Available from: <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death>. Accessed October 24, 2024.
2. 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
3. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med*. 2020;26(7):1017–1032. doi:10.1038/s41591-020-0968-3
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506. doi:10.1016/s0140-6736(20)30183-5
5. Ribes A, Vardon-Bounes F, Mémier V, et al. Thromboembolic events and COVID-19. *Adv Biol Regul*. 2020;77:100735. doi:10.1016/j.jbior.2020.100735
6. Katsoularis I, Fonseca-Rodríguez O, Farrington P, Lindmark K, Fors Connolly AM. Risk of acute myocardial infarction and ischaemic stroke following COVID-19 in Sweden: a self-controlled case series and matched cohort study. *Lancet*. 2021;398(10300):599–607. doi:10.1016/s0140-6736(21)00896-5
7. Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19: nationwide self-controlled cases series and matched cohort study. *BMJ*. 2022;377:e069590. doi:10.1136/bmj-2021-069590
8. Katsoularis I, Jerndal H, Kalucza S, Lindmark K, Fonseca-Rodríguez O, Connolly AF. Risk of arrhythmias following COVID-19: nationwide self-controlled case series and matched cohort study. *Eur Heart J Open*. 2023;3(6):oead120. doi:10.1093/ehjopen/oead120
9. Ollila Hanna M, Fonseca-Rodríguez O, Caspersen IH, et al. How do clinicians use post-COVID syndrome diagnosis? Analysis of clinical features in a Swedish COVID-19 cohort with 18 months' follow-up: a national observational cohort and matched cohort study. *BMJ Public Health*. 2024;2(1):e000336. doi:10.1136/bmjph-2023-000336
10. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377. doi:10.1136/thorax.58.5.377
11. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707–710. doi:10.1007/bf01709751
12. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243–250. doi:10.1056/nejm199701233360402
13. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine; Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992;101(6):1644–1655. doi:10.1378/chest.101.6.1644
14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10):818–829. doi:10.1097/00003246-198510000-00009
15. RCoP L. Royal college of physicians national early warning score (NEWS) 2: standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP. 2017. Available from: <https://www.rcp.ac.uk/improving-care/resources/national-early-warning-score-news-2/>. Accessed July 10, 2025.
16. Marshall JC, Murthy S, Diaz J. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis*. 2020;20(8):e192–e197. doi:10.1016/s1473-3099(20)30483-7
17. World Health Organization. WHO R&D Blueprint novel coronavirus COVID-19 therapeutic trial synopsis. Available from: <https://www.who.int/teams/blueprint/covid-19>. Accessed October 24, 2024.
18. Laugesen K, Ludvigsson JF, Schmidt M, et al. Nordic health registry-based research: a review of health care systems and key registries. *Clin Epidemiol*. 2021;13:533–554. doi:10.2147/clep.S314959
19. Swedish Tax Agency. Personal identification numbers. Available from: <https://www.skatteverket.se/service/ankar/otherlanguages/inenglishengelska/individualsandemployees/livinginsweden/personalidentitynumbers.4.2c1b5cd163796a5c8b4295.html>. Accessed October 24, 2024.
20. Swedish National Board of Health and Welfare. Personal Identification Numbers in health data. Available from: <https://www.socialstyrelsen.se/statistik-och-data/register/>. Accessed October 24, 2024.
21. Swedish Public Health Agency. SmiNet. Available from: <https://www.folkhalsomyndigheten.se/sminet>. Accessed October 24, 2024.
22. Statistics Sweden. Statistics Sweden. Available from: <https://www.scb.se/en/>. Accessed July 10, 2025.
23. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765–773. doi:10.1007/s10654-017-0316-1
24. Swedish Public Health Agency. Swedish national vaccination registry. Available from: <https://www.folkhalsomyndigheten.se/smittskydd-beredskap/vaccinationer/nationella-vaccinationsregistret/>. Accessed July 10, 2025.
25. The Swedish National Board of Health and Welfare. The Swedish National Board of Health And welfare. Available from: <https://www.socialstyrelsen.se/en/>. Accessed July 10, 2025.
26. The Swedish Intensive Care Registry. The Swedish intensive care registry. Available from: <https://www.icuregsw.org/en>. Accessed July 10, 2025.
27. The Swedish National Board of Health and Welfare. The Swedish national cancer register. Available from: <https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-cancer-register/>. Accessed July 10, 2025.
28. Welfare TSNBoHa. The Swedish national cause of death register. Available from: <https://www.socialstyrelsen.se/en/statistics-and-data/registers/national-cause-of-death-register/>. Accessed July 10, 2025.
29. The Swedish National Board of Health and Welfare. The Swedish register of social services for the elderly and persons with disabilities. Available from: <https://www.socialstyrelsen.se/statistik-och-data/register/aldre-och-personer-med-funktionsnedsattning/>. Accessed July 10, 2025.
30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
31. Swedish Association of Local Authorities and Regions. Classification of Swedish municipalities. Available from: <https://skr.se/en/skr/tjanster/kommunerochregioner/faktakommunerochregioner/kommungruppsindelning.2051.html>. Accessed October 24, 2024.

32. Santosa A, Oras J, Li H, Nwaru C, Kirui B, Nyberg F. Survival of critically ill COVID-19 patients in Sweden during the first two and a half years of the pandemic. *Crit Care Med.* **2024**;52(8):1194–1205. doi:10.1097/ccm.0000000000006271
33. Uusküla A, Jürgenson T, Pisarev H, et al. Long-term mortality following SARS-CoV-2 infection: a national cohort study from Estonia. *Lancet Regional Health.* **2022**;18:100394. doi:10.1016/j.lanepe.2022.100394
34. Larsson E, Brattström O, Agvald-öhrman C, et al. Characteristics and outcomes of patients with COVID-19 admitted to ICU in a tertiary hospital in Stockholm, Sweden. *Acta Anaesthesiologica Scandinavica.* **2021**;65(1):76–81. doi:10.1111/aas.13694
35. Hägglöf E, Bell M, Zettersten E, Engerström L, Larsson E. Long-term survival after intensive care for COVID-19: a nationwide cohort study of more than 8000 patients. *Ann Intens Care.* **2023**;13(1):76. doi:10.1186/s13613-023-01156-3
36. Gustafsson PE, San Sebastian M, Fonseca-Rodriguez O, Fors Connolly A-M. Inequitable impact of infection: social gradients in severe COVID-19 outcomes among all confirmed SARS-CoV-2 cases during the first pandemic wave in Sweden. *J Epidemiol Community Health.* **2022**;76(3):261. doi:10.1136/jech-2021-216778
37. Rostila M, Cederström A, Wallace M, Aradhya S, Ahrne M, Juárez SP. Inequalities in COVID-19 severe morbidity and mortality by country of birth in Sweden. *Nat Commun.* **2023**;14(1):4919. doi:10.1038/s41467-023-40568-4
38. The-Statistical-Agencies-of-the-Nordic-Countries. The Nordics during the first phases of COVID-19. **2022**. Available from: <https://www.scb.se/contentassets/c63c858f7c014073bc209edda9c4daf2/the-nordics-and-covid-19.pdf>. Accessed July 10, 2025.

Clinical Epidemiology

Publish your work in this journal

Clinical Epidemiology is an international, peer-reviewed, open access, online journal focusing on disease and drug epidemiology, identification of risk factors and screening procedures to develop optimal preventative initiatives and programs. Specific topics include: diagnosis, prognosis, treatment, screening, prevention, risk factor modification, systematic reviews, risk & safety of medical interventions, epidemiology & biostatistical methods, and evaluation of guidelines, translational medicine, health policies & economic evaluations. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use.

Submit your manuscript here: <https://www.dovepress.com/clinical-epidemiology-journal>

Dovepress
Taylor & Francis Group