What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study in eleven Dutch hospitals

Supplemental information

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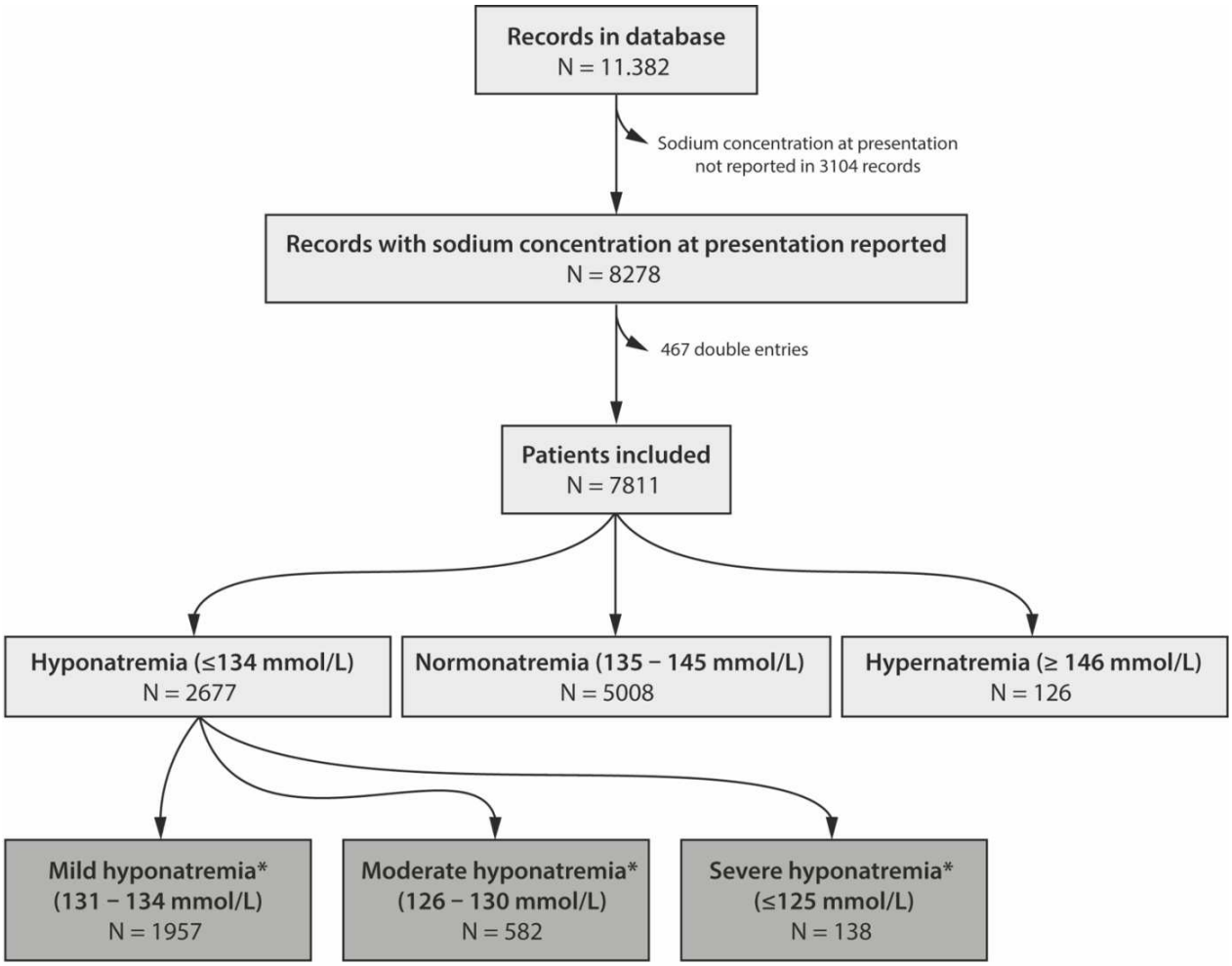


Supplemental Figure 1. Flow chart of included patients. Sodium concentrations indicate corrected serum sodium concentrations at hospital presentation * indicates the subgroup analysis as provided in the supplemental information.

Supplemental Table 1 – Subgroup analysis of patient characteristics

	Na 135 – 145 mmol/L N = 5008	Na ≤134 mmol/L N = 2677	Na 131 – 134 mmol/L N = 1957	Na 126 – 130 mmol/L N = 582	Na ≤125 mmol/L N = 138
Sex assigned at birth (N (%))	♂ 2946 (58.8 %) ♀ 2060 (41.2 %)	♂ 1673 (62.5%) ** ♀ 1003 (37.5%)	♂ 1249 (63.9%) *** ♀ 707 (36.1%)	♂ 363 (62.4%) ♀ 219 (37.6%)	♂ 61 (44.2%) *** ♀ 77 (55.8%)
Age (median age in years (IQR))	N = 5008 66.1 (55.0-76.0)	N = 2675 67.0 (58.0-77.0) **	N = 1956 67.0 (57.0 – 76.0)	N = 581 68.1 (60.0 – 78.0) ***	N =138 70.6 (62.0 – 79.3) ***
BMI (median BMI in kg/m^2 (IQR))	N = 3374 27.7 (24.6 – 31.6)	N = 1740 27.2 (24.2 – 31.1) **	N = 1271 27.4 (24.4 – 31.5)	N = 379 26.3 (23.4 – 30.3) ***	N = 90 26.9 (23.7 – 30.9)
Order 'Do not intubate' (N (%))	796 / 2469 (32.2 %)	440 / 1442 (30.5 %)	304 / 1043 (29.1 %)	108 / 322 (33.5 %)	28 / 77 (36.4 %)
Sodium (mean corrected serum level in mmol/L (IQR))	138.02 (136.42 – 140.0)	132.59 (130.72 – 134.00) ***	133.3 (132.28 – 134.19) ***	129.42 (128.04 – 130.22) ***	123.94 (121.17 – 125.0) ***
Chronic cardiac disease (N (%))	1334 / 4982 (26.8 %)	760 / 2666 (28.5%)	541 / 1948 (27.8 %)	187 / 581 (32.2 %)	32 / 137 (23.4 %)
Hypertension (N (%))	1889 / 4586 (41.2 %)	1055 / 2374 (44.4 %) **	749 / 1735 (43.2 %)	240 / 520 (46.2 %)	66 / 119 (55.5 %) **
Chronic pulmonary disease (N (%))	844 / 4979 (17.0 %)	466 / 2662 (17.5 %)	328 /1945 (16.9 %)	111 / 580 (19.1 %)	27 / 137 (19.7 %)
Chronic kidney disease (N (%))	491 / 4587 (10.7 %)	329 / 2379 (13.8 %) ***	220 / 1738 (12.7 %)	92 / 522 (17.6 %) ***	17 / 119 (14.3 %)
Moderate to severe liver disease (N (%))	50 / 4972 (1.0 %)	30 / 2662 (1.1%)	25 / 1947 (1.3%)	3 / 579 (0.5 %)	2 / 136 (1.5%)
Diabetes (N (%))	1261 / 4972 (25.4 %)	664 / 2662 (24.9 %)	481 / 1946 (24.7 %)	148 / 579 (25.6 %)	35 / 137 (25.5 %)
Immunosuppressives (N (%))	295 / 4445 (6.6 %)	192 / 2283 (8.4 %) **	129 / 1669 (7.7 %)	56 / 497 (11.3 %) **	7 / 117 (6.0 %)
Thiazide diuretics (N (%))	394 / 4994 (7.9 %)	258 / 2671 (9.7 %) **	186 / 1953 (9.5 %)	55 / 580 (9.5 %)	17 / 138 (12.3 %)
Loop diuretics (N (%))	389 / 4994 (7.8 %)	187 / 2671 (7.0 %)	128 / 1953 (6.6 %)	50 / 580 (8.6 %)	9 / 138 (6.5 %)
SSRIs (N (%))	164 / 4994 (3.3 %)	78 / 2671 (2.9 %)	53 / 1953 (2.7%)	15 / 580 (2.6%)	10 / 138 (7.2 %)

*BMI = body mass index; IQR = interquartile range; % = percentage of patients in this group with indicated characteristic; SSRI = Selective Serotonin Reuptake inhibitor. SNRI = Selective Serotonin and Noradrenalin Reuptake inhibitor. Significance was assessed using a Kruskal-Wallis test with post-hoc correction (for numerical data; non-normally distributed) or Chi-square test (for categorical data). p – values for all groups indicate the adjusted significance after post-hoc correction when compared to the normonatremia group. * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*

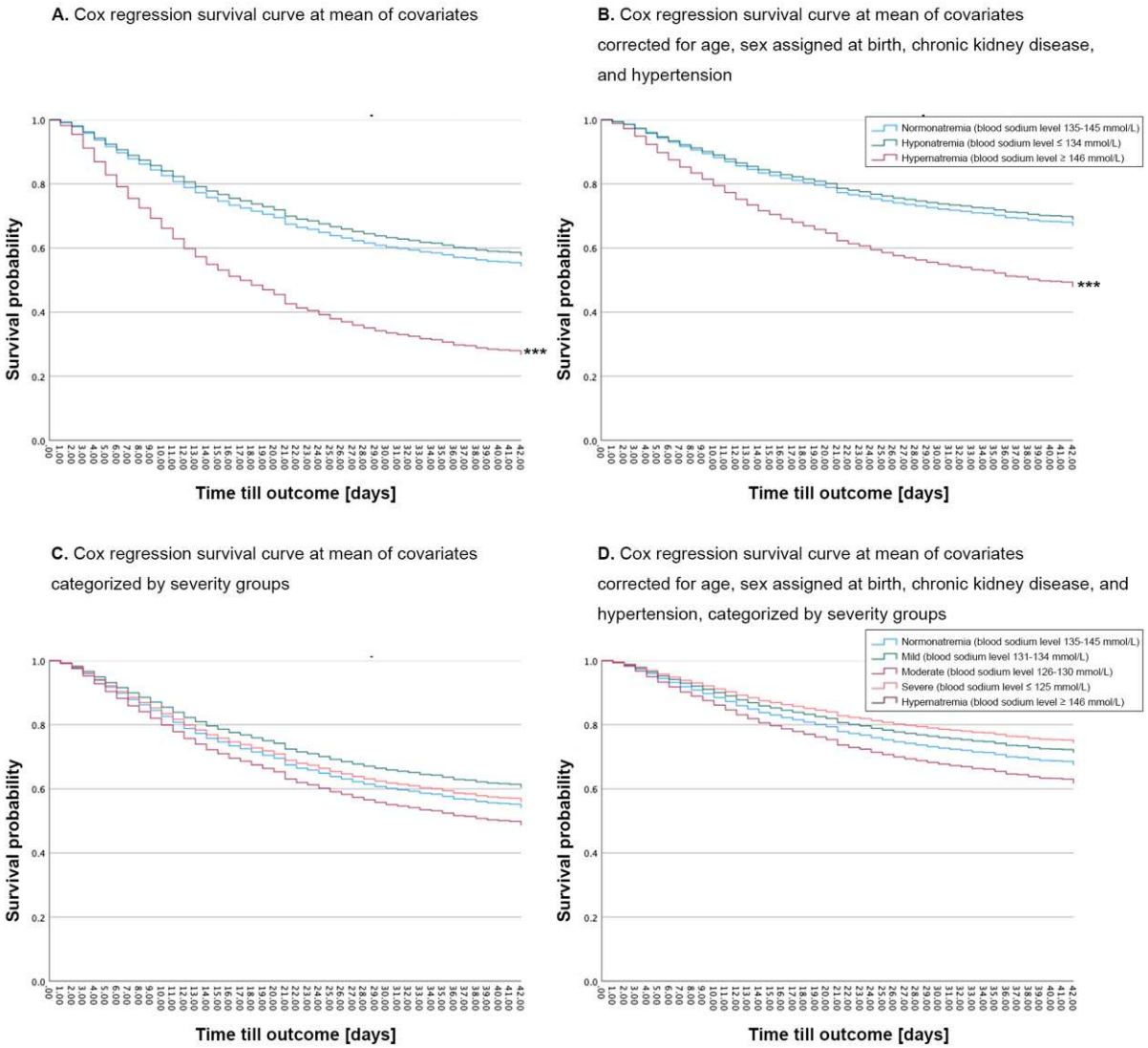
Supplemental Table 2 – Definitions for comorbidities

Comorbidity	**Included diseases**
Chronic pulmonary disease	Alpha-1 trypsin deficiency; asbestosis; cryptogenic organizing pneumonia; lymphangioeiomyomatosus; lung disease immuno-deficiency and chromosome breakage syndrome; bronchopulmonary dysplasia; primary ciliary dyskinesia; bronchiectasis; cystic fibrosis; chronic bronchitis or emphysema; lung fibrosis; sarcoidosis; obstructive sleep apnea; pulmonary hypertension
Chronic cardiac disease	**Chronical heart disease:** Myocardial infarction; Cardiac arrhythmias (AVNRT, atrial fibrillation, (supra)ventricular tachycardia, ventricular tachycardia, brugada syndrome, sick sinus syndrome, wolf parkinson white syndrome; decompensated heart failure, cardiomyopathy; valve disease (aortic valve stenosis, aortic valve insufficiency **Congential heart disease:** aortic valve insufficiency or aortic valve stenosis; Atrial septal defect or ventricular septal defect; hypoplastic left heart syndrome; Ebstein's anomaly; patent ductus arteriosis; tetralogy of Fallot; transposition of the great vessels
Chronic kidney disease	Acute tubulointerstitial nephritis; hemolytic uremic syndrome (HUS); amyloidosis; Anti-glomerular basement membrane disease; bartter syndrome; kidney damage due to medication, chronic bladder infections / kidney infections / diabetes, high blood pressure, arteriosclerosis; cryoglobulinemia, renal cystic disease; cystinosis; dense deposit disease (DDD); Focal segmental glomerulosclerosis (FSGS); Gitelman syndrome; glomerulonephritis; HNF1beta associated kidney disease; renal fusion (horseshoe kidney); IgA nephropathy; medullary sponge kidney; membranous nephropathy; minimal change disease; solitary kidney; Nail-patella syndrome (NPS); nephrogenic diabetes insipidus; nephroptosis; nephrotic syndrome; renal angiolipoma; renal cell carcinoma; primary hyperoxaluria; reflux nephropathy; atrophic kidney; scleroderma; lupus nephritis; Alport's syndrome; systemic vasculitis
Moderate to severe liver disease	Liver disease that caused cirrhosis (e.g. Budd Chiari, hemochromatosis, hepatitis, Wilson's disease)

Supplemental Table 3 – Subgroup analysis of signs and symptoms

Signs and symptoms	Na 135 – 145 mmol/L N = 3206	Na ≤134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na ≤125 mmol/L N = 92
Nausea / vomiting (N (%))	1150 / 4129 (27.9 %)	679 / 2273 (29.9 %)	490 / 1663 (29.5 %)	151 / 499 (30.3 %)	38 / 111 (34.2%)
Diarrhea (N (%))	1146 / 4157 (27.6 %)	804 / 2298 (35.0%) ***	574 / 1686 (34.0 %) ***	180 / 501 (35.9%) ***	50 / 111 (45.0 %) ***
Anosmia (N (%))	352 / 3330 (10.6 %)	244 / 1904 (12.8 %)**	174 / 1395 (12.5 %)	62 / 420 (14.8 %)	8 / 89 (9.0 %)
Confusion (N (%))	651 / 4381 (14.9 %)	311 / 2319 (13.4%)	207 / 1688 (12.3 %)	78 / 511 (15.3 %)	26 / 120 (21.7 %)
Seizures (N (%))	31 / 3452 (0.9 %)	10 / 1977 (0.5%)	6 / 1448 (0.4 %)	2 / 434 (0.5 %)	2 / 95 (2.1 %)
FiO2 (median fraction (IQR))	N = 2084 0.36 (0.28 – 0.50)	N = 1159 0.36 (0.28 – 0.50)	N = 848 0.36 (0.28 – 0.48)	N = 258 0.36 (0.32 – 0.60)	N = 53 0.36 (0.31 – 0.75)
SBP (mean SBP in mmHg (SD))	N = 2648 132 (± 22)	N = 4971 135 (±23)***	N = 1934 132 (±22) ***	N = 578 132 (±22)**	N = 136 138 (±27)
HR (mean HR in BPM (SD))	N = 4965 91 (±20)	N = 2661 92 (±18) **	N = 1946 92 (±18) *	N = 580 92 (±18)	N = 135 90 (±19)
Disturbed capillary refill (N (%))	93 / 1369 (6.8 %)	81 / 863 (9.4 %)	51 / 614 (8.3 %)	27 / 206 (13.1 %)	3 / 43 (7.0 %)
Blood urea level (median level n mmol/L (IQR))	N = 4776 6.2 (4.5 – 9.2)	N = 2549 6.3 (4.5 – 9.3)	N = 1892 6.3 (4.6 – 9.1)	N = 559 6.2 (4.5 – 10.2)	N = 128 5.5 (4.2 – 9.8)
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 4983 68 (46 – 94)	N = 2656 64 (45 – 90) ***	N = 1944 64 (46 – 89) ***	N = 575 63 (41 – 90) ***	N = 137 79 (46 – 92)
CT-severity score (mean score (SD))	N = 1401 12.1 (±5.6)	N = 909 12.4 (±5.5)	N = 684 12.3 (±5.4)	N = 190 12.6 (±5.4)	N = 35 12.5 (±6.7)
Blood CRP level (median level in mg/L (IQR))	N = 4939 70.8 (28.0 – 131)	N = 2646 93.1 (49.0 – 154) ***	N = 1933 93.0 (48.2 – 151) ***	N = 577 103 (54.6 – 166) ***	N = 136 82.5 (36.0 – 145)
Blood LDH level (median level in U/L (IQR))	N = 4226 323 (247 – 426)	N = 2238 349 (268 – 471) ***	N = 1651 346 (269 – 467) ***	N = 479 361 (269 – 482) ***	N = 108 331 (240 – 543)
Modified early warning score (MEWS) (median score (IQR))	N = 4055 3.0 (2.0 – 4.0)	N = 2337 3.0 (2.0 – 4.0) ***	N = 1709 3.0 (2.0 – 4.0) ***	N = 509 3.0 (2.0 – 4.0)	N = 119 3.0 (2.0 – 4.0)
Quick sequential organ failure assessment (median score (IQR))	N = 4131 1.0 (0.0 – 1.0)	N = 2373 (0.0 – 1.0)	N = 1735 1.0 (0.0 – 1.0)	N = 517 1.0 (0.0 – 1.0)	N = 121 1.0 (0.0 – 1.0)

*SBP = systolic blood pressure; HR = heart rate; CKD-epi = chronic kidney disease Epidemiology Collaboration BPM = beats per minute; IQR = interquartile range; SD = standard deviation; CRP = c-reactive protein; LDH = lactate dehydrogenase; % = percentage of patients in this group with indicated characteristic. Significance was assessed using a Kruskal wallis test with post-hoc correction (for numerical data) or Chi-square test (for categorical data). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*



Supplemental Figure 2. Cox proportional survival curves at the mean of covariates for (A) unadjusted 6-week mortality categorized by normo-, hypo-, and hypernatremia, (B) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo-, hypo-, and hypernatremia, (C) unadjusted 6-week mortality stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia, and (D)) 6-week mortality adjusted for age, sex assigned at birth, a history of chronic kidney disease, and a history of hypertension stratified in normo- and hypernatremia and mild, moderate, and severe hyponatremia. * Indicates a p-value <0.05, *** indicates a p-value <0.001

Supplemental Table 4 – Subgroup analysis of outcome and complications

Outcome	Na 135 – 145 mmol/L N = 3206	Na ≤134 mmol/L N = 1821	Na 131 – 134 mmol/L N = 1346	Na 126 – 130 mmol/L N = 383	Na ≤125 mmol/L N = 92
Duration of admission (median days (IQR))	N = 4116 7 (3 – 14)	N = 2372 7 (4 – 16) ***	N = 1735 7 (4 –15) **	N = 514 8 (4 – 18)*	N123 8 (3 – 18)
Death or palliative discharge (N (%))	729 / 4568 (16.0 %)	405 / 2360 (17.2 %) [A]OR 1.042 (0.906 – 1.200)	269 / 1723 (15.6 %)	115 / 518 (22.2 %)	21 / 119 (17.6 %)
ICU-admission (N (%), 'do not intubate' excluded	710 / 3778 (18.8 %)	439 / 1923 (22.8 %) [A]OR 1.274 (1.112 – 1.458)***	314 / 1422 (22.1 %) [A]OR 1.205 (1.036 – 1.401)*	104 / 410 (25.4 %) [A]OR 1.487 (1.170 – 1.889)***	21 / 91 (23.1 %) [A]OR 1.431 (0.868 – 2.360)
Duration of ICU-admission (days (IQR)) 'do not intubate' excluded	N = 437 10 (4 – 19)	N = 299 8 (3 - 19) p = 0.356	N = 215 8 (3 – 20)	N = 68 8 (4 – 18)	N = 16 9 (4 – 21)
Invasive ventilation (N (%)), 'do not intubate' excluded	623 / 3706 (16.8 %)	352 / 1889 (18.6 %) [A]OR 1.122 (0.970 – 1.298)	250 / 1396 (17.9 %)	85 / 402 (21.1 %)	17 / 91 (18.7 %)
Discharge alive within 42 days; N indicating the number of non-censored cases	N = 2747	N = 1527 [A]HR 0.955 (0.897 – 1.017) p = 0.154	N = 1153	N = 302	N = 72
Use of tocilizumab, sarilumab, or anakinra (N (%))	199 / 1245 (16.0%)	134 / 688 (19.5%) [A]OR 1.256 (0.984 – 1.604) p = 0.068	91 / 480 (19.0 %)	36 / 169 (21.3 %)	7 / 39 (17.9%)
Complications	**Na 135 – 145 mmol/L N = 3206**	**Na ≤134 mmol/L N = 1821**	**Na 131 – 134 mmol/L N = 1346**	**Na 126 – 130 mmol/L N = 383**	**Na ≤125 mmol/L N = 92**
Bacterial pneumonia (N (%))	501 / 4307 (11.6 %)	289 / 2212 (13.1 %) [A]OR 1.123 (0.962 – 1.312)	207 / 1619 (12.8 %)	72 / 483 (14.9 %)	10 / 110 (9.1 %)
Aspergillosis pneumonia (N (%))	83 / 3456 (2.4 %)	67 / 1915 (3.5 %) [A]OR 1.436 (1.034 – 1.993)	49 / 1402 (3.5 %) [A]OR 1.426 (0.995 – 2.044)	14 / 417 (3.4 %) [A]OR 1.352 (0.759 – 2.410)	4 / 96 (4.2 %) [A]OR 1.839 (0.657 – 5.148)
ARDS (N (%))	404 / 4323 (9.3 %)	224 / 2223 (10.1 %) [A]OR 1.081 (0.909 – 1.286)	161 /1627 (9.9 %)	52 / 486 (10.7 %)	11 / 110 (10.0 %)
Treatment for septic shock (N (%)) [&]	135 / 4175 (3.2 %)	94 / 2153 (4.4 %) [A]OR 1.326 (1.013 – 1.737)*	66 / 1570 (4.2 %) [A]OR 1.274 (0.943 – 1.721)	25 / 478 (5.2 %) [A]OR 1.570 (1.012 – 2.438)*	3 / 105 (2.9%) [A]OR 0.920 (0.287 – 2.946
Congestive heart failure (N (%))	125 / 4352 (2.9 %)	64 / 2235 (2.9 %) [A]OR 0.946 (0.696 – 1.287)	34 / 1637 (2.1%)	23 / 488 (4.7 %)	7 / 110 (6.4 %)
Physical decline (N (%))	950 / 4126 (23.0 %)	576 / 2116 (27.2 %) [A]OR 1.221 (1.082 – 1.377)**	414 / 1544 (26.8 %) [A]OR 1.206 (1.054 – 1.380)**	136 / 468 (29.1 %) [A]OR 1.303 (1.053 – 1.614)*	26 / 104 (25.0 %) [A]OR 1.059 (0.674 – 1.666)

Delirium (N (%))	451 / 4146 (10.5 %)	237 / 2136 (11.1 %) [A]OR 0.987 (0.833 - 1.170)	157 / 1557 (10.1 %)	62 / 474 (13.1 %)	18 / 105 (17.1 %)

*ICU = Intensive care unit; ARDS = acute respiratory distress syndrome; OR = odds ratio; [A]OR = adjusted odds ratio; odds ratio corrected for sex assigned at birth and age; IQR = interquartile range. [#]Uncorrected for sex assigned at birth and age [&] Treatment for septic shock was defined as the need for vasopressors in order to maintain mean arterial blood pressure >65 mmHg and blood lactate level >2 mmol/L, in the absence of other causes including hypovolemia. Significance was assessed using a Kruskal wallis test with post-hoc correction (time to discharge alive) or logistic regression (all other values). * Indicates a p-value <0.05, ** indicates a p-value <0.01, *** indicates a p-value <0.001*

Supplemental Table 5 – Characteristics of patients with the order 'do not intubate'

	Order 'do not intubate'	**No order 'do not intubate'**	**p-value**
Sex assigned at birth (N (%))	♀ 531/ 1576 (33.7 %) ♂ 743 / 2388 (31.1 %)	♀ 1045 / 1576 (66.3 %) ♂ 1645 / 2388 (68.9 %)	p = 0.095
Age (median age in years (IQR))	79 (73 – 84)	62 (53 -71)	p < 0.001
BMI (median BMI in kg/m^2 (IQR))	26.2 (23.1 – 30.1)	27.9 (25.0 – 31.9)	p < 0.001
Corrected sodium level at presentation in mmol/L (IQR))	135.9 (± 4.5)	136.6 (±5.1)	p < 0.001
ICU admission (N (%))	83 / 1275 (6.5 %)	781 / 2690 (29 %)	p < 0.001
Chronic pulmonary disease (N (%))	361 / 1270 (28.4 %)	359 / 2680 (13.4%)	p < 0.001
Asthma (N (%))	95 / 1269 (7.5 %)	256 / 2678 (9.6%)	p = 0.036
Chronic obstructive pulmonary disease (N (%))	125 / 267 (46.8 %)	80 / 293 (27.3 %)	p < 0.001
Chronic kidney disease (N (%))	259 / 1270 (20.4 %)	250 / 2681 (9.3%)	p < 0.001
Chronic cardiac disease (N (%))	637 / 1266 (50.3 %)	564 / 2683 (21.0%)	p < 0.001
Hypertension (N (%))	755 / 1270 (59.4 %)	1051 / 2685 (39.1 %)	p < 0.001
Moderate to severe liver disease (N (%))	21 / 1267 (1.7 %)	28 / 2680 (1.0 %)	p = 0.123
Diabetes (N (%))	457 / 1270 (36.0 %)	679 / 2680 (25.3 %)	p < 0.001
Neoplasm (N (%))	156 / 1273 (12.3 %)	130 / 2682 (4.8 %)	p < 0.001

BMI = Body Mass Index; IQR = interquartile range. Significance was assessed using a Student's t-test (for normally distributed numerical data), Mann-Whitney test (for non-normally distributed numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

Supplemental Table 6 – Patient characteristics, signs and symptoms, outcome measures, and complications of patients with hyponatremia (Na ≤ 134 mmol/L) that did not use diuretics stratified based on their urinary sodium excretion.

Patient characteristics	**Urinary sodium excretion < 30 mmol/L** % or IQR N = 72	**Urinary sodium excretion ≥ 30 mmol/L** % or IQR N = 73	**p - value**
Age (median age in years (IQR))	N = 72 67 (56 – 74)	N = 73 69 (59 – 76)	p = 0.47
Sex assigned at birth (N (%))	♂ 38 (53%) ♀ 34 (47%)	♂ 43 (59%) ♀ 30 (41%)	p = 0.51
Vomiting/nausea (N (%))	32 / 71 (45.1 %)	19 / 67 (28.4 %)	p = 0.05
Diarrhea (N (%))	26 / 67 (38.8 %)	28 / 68 (41.2 %)	p = 0.86
Heart rate (mean HR in BPM (SD))	N = 71 89.7 (± 16.3)	N = 72 93.1 (±18.9)	p = 0.25
Systolic blood pressure (mean SBP in mmHg (SD))	N = 70 135 (± 24.8)	N = 71 137 (±24.1)	p = 0.68
Disturbed capillary refill (N (%))	3 / 27 (11.1 %)	4 /31 (12.9 %)	p = 1.00
eGFR rate using 2021 CKD-epi creatinine equation in (median clearance in ml/min/1.73 m^3 (IQR))	N = 71 67 (49 – 90)	N = 73 71 (32 – 92)	p = 0.49
CRP (median level in mmol/L (IQR))	N = 70 111 (52.5 – 163)	N = 71 70 (35.0 – 154)	**p = 0.028**
LDH (median level in U/L (IQR))	N = 57 351 (270 – 491)	N = 61 273 (227 – 434)	**p = 0.021**
CT-severity score (median score (IQR))	N = 33 11.0 (7.0 – 15.0)	N = 40 12.0 (6.0 – 16.8)	p = 0.86
Outcome			
Death or palliative discharge (N (%))	14 / 72 (19.4%)	18 / 73 (24.7 %)	p = 0.55
ICU-admission (N (%), 'do not intubate' excluded	24 / 65 (36.9 %)	25 / 61 (41.0 %)	p = 0.72
Invasive ventilation (N (%)), 'do not intubate' excluded	18 / 64 (28.1 %)	23 / 60 (38.3 %)	p = 0.26

CRP = C-reactive protein; LDH = lactate dehydrogenase; CT = computed tomography; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; CKD-epi = chronic kidney disease Epidemiology Collaboration; IQR = interquartile range; SD = standard deviation. Significance was assessed using a Student's t-test (for normally distributed numerical data), Mann-Whitney test (for non-normally distributed numerical data) or Chi-square test (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.

Supplemental Table 7 – Patient characteristics, signs and symptoms, outcome measures, and complications for each SARS-CoV-2 variant

	Initial	**Alpha**	**Delta**	**Omicron**	**p-value**
Sex assigned at birth (N (%))	♀ 2431 (39.3 %) ♂ 3754 (60.7 %)	♀ 322 (40.3 %) ♂ 477 (59.7 %)	♀ 300 (42.9 %) ♂ 399 (57.1 %)	♀ 52 (42.6 %) ♂ 70 (57.4 %)	p = 0.266
Age (median age in years (IQR))	67 (57 – 77)	63 (53 – 73)	65 (52 – 77)	71 (59 – 76)	p <0.001 for alpha vs. initial / omicron p = 0.012 for alpha vs. delta p = 0.006 for delta vs. initial
BMI (median BMI in kg/m^2 (IQR))	27.4 (24.3 – 31.2)	27.9 (24.9 – 32.9)	27.7 (24.4 – 32.2)	26.8 (23.8 – 30.4)	p = 0.012 for alpha vs. initial
Corrected sodium level at presentation in mmol/L (IQR))	136.5 (134.0 – 139.0)	136.0 (133.3 – 138.4)	136.1 (133.0 – 138.6)	136.1 (133.8 – 138.9)	p <0.001 for alpha / delta vs. initial
Patients with hyponatremia that presented with diarrhea or vomiting (N (%))	1524 / 3327 (45.8 %)	191 / 398 (48.0 %)	130 / 389 (33.4 %)	27 / 73 (37.0 %)	p < 0.001 for delta vs. alpha / initial
Patients with hyponatremia that used diuretics at presentation (N (%))	348 / 2042 (17.0 %)	46 / 305 (15.1 %)	60 / 283 (21.2 %)	18 / 40 (45.0 %)	p < 0.001 for omicron vs. initial / alpha / delta
Patients with hyponatremia that complied to the definition of SIADH (N (%))	12 / 94 (12.8 %)	0 / 2 (0 %)	0 / 4 (0 %)	0 / 0 (0 %)	p = 0.647
Patients with hyponatremia of unknown etiology (N (%))	939 / 2045 (45.9 %)	142 / 308 (46.1 %)	121 / 283 (42.8 %)	8 / 40 (20 %)	p = 0.009 for omicron vs. initial / alpha / delta

BMI = body mass index; SIADH = syndrome of inappropriate antidiuretic hormone secretion; IQR = interquartile range. Significance was assessed using a Kruskal wallis test with post-hoc correction (for numerical data) or logistic regression (for categorical data). p – values for all groups indicate the 2-tailed significance between the two groups.