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Burden of disease in patients hospitalised with COVID-19 during the first and second pandemic wave in Switzerland: a nationwide cohort study

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Summary

AIM OF THE STUDY: The first and second waves of the COVID-19 pandemic led to a tremendous burden of disease and influenced several policy directives, prevention and treatment strategies as well as lifestyle and social behaviours. We aimed to describe trends of hospitalisations with COVID-19 and hospital-associated outcomes in these patients during the first two pandemic waves in Switzerland.

METHODS: In this nationwide retrospective cohort study, we used in-hospital claims data of patients hospitalised with COVID-19 in Switzerland between January 1st and December 31st, 2020. First, stratified by wave (first wave: January to May, second wave: June to December), we estimated incidence rates (IR) and rate differences (RD) per 10,000 person-years of COVID-19-related hospitalisations across different age groups (0–9, 10–19, 20–49, 50–69, and ≥70 years). IR was calculated by counting the number of COVID-19 hospitalisations for each patient age stratum paired with the number of persons living in Switzerland during the specific wave period. Second, adjusted odds ratios (aOR) of outcomes among COVID-19 hospitalisations were calculated to assess the association between COVID-19 wave and outcomes, adjusted for potential confounders.

RESULTS: Of 36,517 hospitalisations with COVID-19, 8,862 (24.3%) were identified during the first and 27,655 (75.7%) during the second wave. IR for hospitalisations with COVID-19 was highest during the second wave and among patients above 50 years (50–69 years: first wave: 31.49 per 10,000 person-years; second wave: 62.81 per 10,000 person-years; RD 31.32 [95% confidence interval [CI]: 29.56 to 33.08] per 10,000 person-years; IRR 1.99 [95% CI: 1.91 to 2.08]; ≥70 years: first wave: 88.59 per 10,000 person-years; second wave: 228.41 per 10,000 person-years; RD 139.83 [95% CI: 135.42 to 144.23] per 10,000 person-years; IRR 2.58 [95% CI: 2.49 to 2.67]). While there was no difference in hospital readmission, when compared with the first wave, patients hospitalised during the second wave had a lower probability of death (aOR 0.88 [95% CI: 0.81 to 0.95], ARDS (aOR 0.56 [95% CI: 0.51 to 0.61]), ICU admission (aOR 0.66 [95% CI: 0.61 to 0.70]), and need for ECMO (aOR 0.60 [95% CI: 0.38 to 0.92]). LOS was –16.1 % (95% CI: –17.8 to –14.2) shorter during the second wave.

CONCLUSION: In this nationwide cohort study, rates of hospitalisations with COVID-19 were highest among adults older than 50 years and during the second wave. Except for hospital readmission, the likelihood of adverse outcomes was lower during the second pandemic wave, which may be explained by advances in the understanding of the disease and improved treatment options.

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Introduction

In 2020, Switzerland faced two waves of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pandemic in spring and winter, respectively. At the beginning of the first wave, many European countries reached their capacity limits of acute and/or intensive care beds for COVID-19 affected patients requiring inpatient care [1]. Therefore, hospitals throughout Europe were forced to restore their capacity by postponing elective treatments and non-emergency surgeries [2, 3]. To address the threat, Swiss authorities introduced public health demands and restrictions to limit the spread of the new virus. While during the first wave, policy interventions included non-pharmacological mitigation measures such as national closures of borders, schools, non-essential stores and businesses with a nationwide lockdown mid of March 2020, [4] during the second wave, the main non-pharmacological measures included social distancing, increased testing, and restricted mobility [5, 6].

With cumulating evidence during the second wave, the antiviral remdesivir was prescribed more frequently [7–9]. In addition, dexamethasone was prescribed to most hospitalised patients needing oxygen therapy during the second

wave [10]. Moreover, different strategies were applied regarding the hospitalisation of infected people. While, during the first wave, most infected people were hospitalised, even with only minor symptoms, this was no longer the case during the second wave, where criteria for hospitalisation were far more restrictive and based on clinical parameters [11]. Regardless, given the many infected people, the absolute number of hospitalisations during the second wave were higher.

As both the number of hospitalisations with COVID-19 and treatment options varied substantially between the first and second wave [12], we sought to evaluate epidemiological trends of COVID-19 related hospitalisations and corresponding in-hospital outcomes across different age groups using clinical routine data from Switzerland.

Methods

Study design

This analysis was conducted using a nationwide cohort of patients hospitalised with COVID-19 in Switzerland between January 1st and December 31st 2020. Hospitalisation data was provided by the Swiss Federal Statistical Office (FSO, Neuchâtel, Switzerland), based on a nationwide compulsory full census of Swiss hospitals. The dataset includes all Swiss inpatient discharge records from general hospitals for acute somatic care. Individual-level data on patient demographics, healthcare utilisation, hospital typology, medical diagnoses, clinical procedures, and in-hospital patient outcomes were provided. A multi-step anonymisation procedure ensured patient confidentiality, and an unique patient identifier was used to ascertain re-hospitalisations. Medical diagnoses were coded using the International Classification of Disease version 10, German Modification (ICD-10-GM) codes. Open-source census data from the FSO on the Swiss population size, stratified by age and year, and data from the Swiss Federal Office of Public Health (FOPH) on the number of positive tests for SARS-CoV-2, stratified by age and period were obtained to calculate population-based incidence rates (IR) of hospitalisation with COVID-19. The institutional review board of Northwestern and Central Switzerland (EKNZ) waived the need for an ethical authorisation due to the use of exclusively anonymised data (EKNZ Project-ID: Req-2021-01397). This study adheres to the "Strengthening The Reporting of Observational Studies in Epidemiology (STROBE)" statement [13].

Case ascertainment and study variables

For this analysis, we included all hospitalisations that were treated with or for COVID-19. Hospitalisations in special clinics (psychiatric clinics, rehabilitation clinics, and other special clinics) were excluded. To identify hospitalisations with COVID-19, we used the following International Statistical Classification of Diseases and Related Health Problems, German Modification (ICD-10-GM) discharge codes at any position: U07.1 and U07.2. Details on all ICD-10-GM codes and Swiss operation classification (CHOP) codes used for the analysis are summarised in Table S1-S3 in the appendix. Comorbidities were measured using the Elixhauser Comorbidity Index [14], and frailty was measured using the Hospital Frailty Score [15].

Outcomes

The primary outcome was the IR of hospitalisation with COVID-19 per 10,000 person-years (PY) with corresponding 95% confidence intervals (CIs) during the first and second waves across the age spectrum. Secondary outcomes comprised of the occurrence of the following in-hospital outcomes during the first and second wave: all-cause in-hospital mortality, acute respiratory distress syndrome (ARDS), length of hospital stay (LOS), intensive care unit (ICU) admission, length of ICU stay, mechanical ventilation, duration of mechanical ventilation, extracorporeal membrane oxygenation (ECMO), and 30-day all-cause hospital readmission. Hospitalisation with COVID-19 and ARDS was defined using ICD-10-GM codes, and the need for ECMO was defined using CHOP codes (table S1-S3 in the appendix). The remaining outcomes were applicable in the dataset provided by the FSO. Analyses of hospital outcomes were stratified by different age groups (0–9, 10–19, 20–49, 50–69, and ≥70 years).Out-of-hospital mortality data was not available in the dataset and could not be linked to the national death registry.

Statistical analysis

Descriptive statistic was calculated for patient demographics, including age, sex, nationality, and insurance status. All baseline characteristics are expressed as mean (standard deviation [SD]), median (interquartile range [IQR]), or frequency (%). Graphical illustration of hospitalisation IR over age spectrum was performed using locally estimated scatterplot smoothing (LOESS). Stratified by waves (first wave: January to May, second wave: June to December), we estimated IR per 10,000 PY with 95% CI, rate differences (RD), and incidence rate ratios (IRR). IR was calculated, allowing multiple hospitalisations for a single person (more than 95% of the patients were hospitalised only once) [16]. These estimates were calculated as the number of individuals with a COVID-19 hospitalisation divided by the sum of "person-time" population at risk in Switzerland, represented by the population size multiplied by the 5-month follow-up during the first wave and by the 7-month follow-up, according to age. To assess the IR of hospitalisation among the overall Swiss population, the denominator was the standard population in 2020 during the first or second waves, respectively. We used the number of people living in Switzerland at the end of 2020 as a surrogate. This information is publicly available and published by the FSO [17]. We aggregated COVID-19 hospitalisations per year of patient age. In detail, we counted the number of COVID-19 hospitalisations for each patient age stratum paired with the published number of persons during the respective wave in Switzerland. Thus, we assumed 5/12 of one person-year for every resident during the first wave and 7/12 of one person-year for every resident during the second wave, ignoring people dying or moving in and out of the country. IR of hospitalisation among those who had a proven SARS-CoV-2 infection were calculated using the overall positively tested population in the denominator. These analyses were performed within the above-mentioned age groups, and the first wave was denoted as a reference.

To explore differences in binary hospital outcomes between the waves and by age groups, we estimated adjusted

odds ratios (aOR) and corresponding 95% CIs using a multivariable logistic regression model. For continuous right-skewed outcomes, we assessed changes in percentage and corresponding 95% CIs using a multiple linear generalised log-gamma regression model. All models were adjusted for age, sex and Elixhauser comorbidity index. The selection of covariates was based on the research question at hand and on knowledge such as what was important to guide hospitalisation criteria during the waves in Switzerland.

We evaluated for heterogeneity in OR estimates across age groups using the Wald test for homogeneity. We performed a risk factor analysis for mortality using univariable and multivariable analyses. All p-values are two-sided and have not been adjusted for multiple testing. Results were considered statistically significant at $p < 0.05$. Statistical analyses were performed with STATA 15.1 (STATA Corp., College Station, TX, USA).

Results

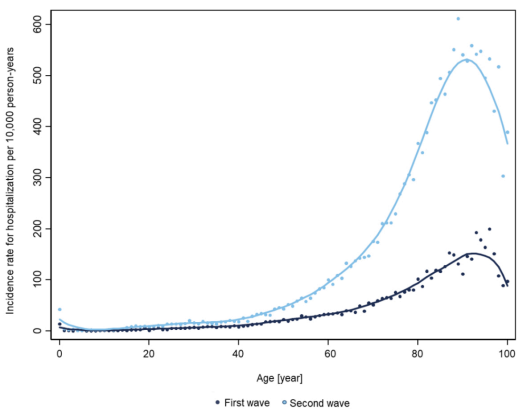
Characteristics of the cohort

From January 1st to December 31st 2020, we identified 36,517 hospitalisations with COVID-19, 8862 (24.3%) during the first and 27,655 (75.7%) during the second wave. Baseline characteristics of the eligible study population stratified by age groups are shown in table 1. Baseline characteristics stratified by waves are summarised in table S4 in the appendix. Overall, the median age was 72 years (IQR, 58 to 82), 57.3% were male, 74.8% were Swiss residents, and 13.8% had supplementary health care insurance. The majority of hospitalisations was observed in patients aged older than 45 years. Among those, we observed an overall high burden of comorbidities, with similar distribution during the first and second waves.

Hospitalisation rates of patients with COVID-19

While IR of hospitalisations during the first and second waves were generally low in children and adolescents, they increased at around the age of 40 years, with a peak in older patients during both waves (figure 1a).

Figure 1a: Age-dependent incidence rates for hospitalisations for COVID-19 among the overall Swiss population per 10,000 person-years during the first wave (dark blue) and second wave (light blue), using locally estimated scatterplot smoothing (LOESS).



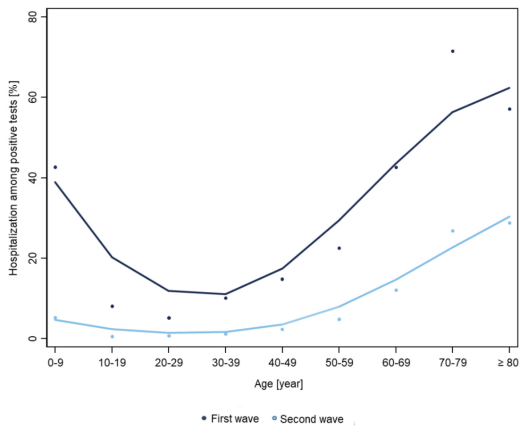
Considering the overall standard population in the denominator, IR were higher during the second wave compared with the first wave. COVID-19 hospitalisation rates were highest in patients above 50 years (50–69 years: first wave: 31.49 per 10,000 person-years; second wave: 62.81 per 10,000 person-years; RD 31.32 [95% CI: 29.56 to 33.08] per 10,000 person-years; ≥70 years: first wave: 88.59 per 10,000 person-years; second wave: 228.41 per 10,000 person-years; RD 139.83 [95% CI: 135.42 to 144.23] per 10,000 person-years) with a strong predominance during the second wave (table 2).

Illustration of hospitalisation IR across the age spectrum among those who were tested positive for SARS-CoV-2 showed different patterns for the first and second wave, with a first peak of hospitalisations among children aged 0 to 9 year and a second peak with a continuous increase of hospitalisations among adults beyond age 50 (figure 1b). While rates of hospitalisation among the overall Swiss population were higher during the second wave (figure 1a), the proportion of hospitalised people among positively tested individuals was higher during the first wave (figure 1b).

In-hospital outcomes between the first and second wave

Among the overall population, 1028 (11.6%) died in hospital during the first wave and 3264 (11.8%) during the second wave, corresponding to lower odds of in-hospital mortality during the second wave (aOR 0.88 [95% CI: 0.81 to 0.95]). Similarly, compared with the first wave, we observed lower numbers of patients with ARDS (1056 [11.9%] vs. 1945 [7.0%], aOR 0.56 [95% CI: 0.51 to 0.61]), ICU admission (1463 [16.5%] vs. 3160 [11.4%], aOR 0.66 [95% CI: 0.61 to 0.70]), in need for mechanical ventilation (1101 [12.4%] vs. 2120 [7.7%], aOR 0.67 [95% CI: 0.58 to 0.78]), and in need for ECMO (38 [0.4%] vs. 46 [0.2%], aOR 0.60 [95% CI: 0.38 to 0.92]) during the second wave. The odds for 30-day all-cause hospital readmission remained similar during the first and second wave (427 [4.8%] vs. 1340 [4.9%], aOR of 0.99 [95% CI: 0.88 to 1.10]) (figure 2). Compared with the first wave, LOS (7.4

Figure 1b: Age-dependent incidence rates for hospitalisations for COVID-19 among the overall SARS-CoV-2 positive tested population per 10,000 person-years during the first wave (dark blue) and second wave (light blue), using locally estimated scatterplot smoothing (LOESS).



[SD 2.7] vs. 6.7 [SD 2.5]) and ICU LOS (6.2 [SD 4.0] vs. 4.1 [SD 3.9]) were shorter during the second wave with a reduction of –16.1% (95% CI: –17.8 to –14.2) and –32.7% (95% CI: –37.2 to –27.9), respectively (figure 3). There

Table 1:
Baseline characteristics stratified by age groups.

		<10 years	10–19 years	20–49 years	50–69 years	≥70 years
Hospitalisations, n		297	275	4,338	11,278	20,329
Wave, n (%)	First wave	73 (24.6)	72 (26.2)	1333 (30.7)	2974 (26.4)	4410 (21.7)
	Second wave	224 (75.4)	203 (73.8)	3005 (69.3)	8304 (73.6)	15,919 (78.3)
Demographics	Age, median (IQR) [years]	0 (0, 2)	16 (14, 18)	40 (32, 46)	61 (56, 65)	80 (75, 86)
	Male sex, n (%)	161 (54.2)	133 (48.4)	2321 (53.5)	7244 (64.2)	11,052 (54.4)
	Swiss nationality, n (%)	181 (60.9)	178 (64.7)	2277 (52.5)	7622 (67.6)	17,058 (83.9)
	Supplementary insurance, n (%)	20 (6.7)	32 (11.6)	308 (7.1)	1248 (11.1)	3432 (16.9)
Admission data	Emergency admission, n (%)	215 (72.4)	221 (80.4)	3692 (85.1)	9831 (87.2)	16,576 (81.5)
	Admission from home, n (%)	277 (93.3)	246 (89.5)	3857 (88.9)	9617 (85.3)	14,675 (72.2)
	Admission to tertiary care hospital: university hospital, n (%)	116 (39.1)	122 (44.4)	1472 (33.9)	2803 (24.9)	4507 (22.2)
	Admission to tertiary care hospital: non-university hospital, n (%)	168 (56.6)	119 (43.3)	2190 (50.5)	6338 (56.2)	11,657 (57.3)
	Admission to secondary care hospital, n (%)	13 (4.4)	34 (12.4)	676 (15.6)	2137 (18.9)	4165 (20.5)
Comorbidities, n (%)	Hypertension	2 (0.7)	4 (1.5)	444 (10.2)	4596 (40.8)	12,481 (61.4)
	Dyslipidemia	0 (0.0)	0 (0.0)	128 (3.0)	1731 (15.3)	4119 (20.3)
	Obesity (BMI ≥ 30.0 kg/m2)	2 (0.7)	6 (2.2)	197 (4.5)	612 (5.4)	559 (2.7)
	Coronary artery disease	2 (0.7)	1 (0.4)	63 (1.5)	1220 (10.8)	4336 (21.3)
	Atrial fibrillation	0 (0.0)	1 (0.4)	31 (0.7)	820 (7.3)	5269 (25.9)
	Congestive heart failure	6 (2.0)	9 (3.3)	64 (1.5)	476 (4.2)	3094 (15.2)
	Peripheral arterial disease	0 (0.0)	0 (0.0)	5 (0.1)	181 (1.6)	1012 (5.0)
	Cerebrovascular disease	1 (0.3)	2 (0.7)	43 (1.0)	357 (3.2)	1233 (6.1)
	Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	17 (0.4)	582 (5.2)	1889 (9.3)
	Bronchial asthma	9 (3.0)	12 (4.4)	247 (5.7)	557 (4.9)	618 (3.0)
	Obstructive sleep apnoea syndrome	1 (0.3)	1 (0.4)	95 (2.2)	669 (5.9)	889 (4.4)
	Chronic kidney disease stage 3 & 4	0 (0.0)	1 (0.4)	36 (0.8)	458 (4.1)	4066 (20.0)
	Chronic kidney disease stage 5 & hemodialysis	1 (0.3)	1 (0.4)	42 (1.0)	294 (2.6)	495 (2.4)
	Solid organ transplant recipient	1 (0.3)	4 (1.5)	64 (1.5)	199 (1.8)	84 (0.4)
	Solid tumour	5 (1.7)	3 (1.1)	88 (2.0)	560 (5.0)	1296 (6.4)
	Liver disease, including cirrhosis	2 (0.7)	6 (2.2)	202 (4.7)	693 (6.1)	660 (3.2)
	Diabetes mellitus type 2	0 (0.0)	1 (0.4)	231 (5.3)	2584 (22.9)	5172 (25.4)
	Diabetes mellitus type 1	1 (0.3)	11 (4.0)	27 (0.6)	57 (0.5)	45 (0.2)
	Haematological malignancy	8 (2.7)	7 (2.5)	60 (1.4)	216 (1.9)	367 (1.8)
	Rheumatoid arthritis	0 (0.0)	1 (0.4)	22 (0.5)	131 (1.2)	324 (1.6)
	Human immunodeficiency virus infection	0 (0.0)	0 (0.0)	31 (0.7)	78 (0.7)	32 (0.2)
	Elixhauser comorbidity index, median (IQR)	0 (0, 1)	0 (0, 1)	1 (0, 2)	2 (1, 3)	3 (2, 4)
Hospital frailty score, n (%)	<5 points	275 (92.6)	249 (90.5)	3870 (89.2)	8390 (74.4)	9647 (47.5)
	5–15 points	21 (7.1)	26 (9.5)	445 (10.3)	2642 (23.4)	8987 (44.2)
	>15 points	1 (0.3)	0 (0.0)	23 (0.5)	246 (2.2)	1695 (8.3)
Outcomes	In-hospital mortality, n (%)	2 (0.7)	0 (0.0)	39 (0.9)	526 (4.7)	3725 (18.3)
	ICU admission, n (%)	23 (7.7)	29 (10.5)	479 (11.0)	2012 (17.8)	2080 (10.2)
	ICU LOS, median (IQR) [days]	3.5 (1.7, 7.6)	2.1 (0.8, 5.8)	3.8 (1.5, 10.5)	6.9 (2.5, 15.7)	4.9 (1.6, 12.6)
	Need for mechanical ventilation, n (%)	14 (4.7)	11 (4.0)	282 (6.5)	1484 (13.2)	1430 (7.0)
	Duration of mechanical ventilation, median (IQR) [days]	2.2 (1.0, 7.5)	2.0 (1.0, 6.3)	7.0 (2.7, 12.3)	8.7 (3.7, 16.0)	6.7 (2.0, 14.3)
	30-days rehospitalisation, n (%)	17 (5.7)	13 (4.7)	203 (4.7)	485 (4.3)	1049 (5.2)

BMI: body mass index; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay

Table 2:
Differences in absolute and relative risk between the first and second COVID-19 waves across age groups.

	Age 0–9 years		Age 10–19 years		Age 20–49 years		Age 50–69		Age ≥70		p of interaction
	First wave	Second wave	First wave	Second wave	First wave	Second wave	First wave	Second wave	First wave	Second wave	
Hospitalisations, n	73	224	72	203	1333	3005	2974	8304	4410	15,919	
Person-years	365,335	511,468	353,958	495,541	1,451,184	2,031,657	944,334	1,322,068	497,815	696,941	
Incidence rate per 10,000 PY	1.99	4.38	2.03	4.10	9.19	14.79	31.49	62.81	88.59	228.41	
Incidence rate difference (95% CI)	Ref.	2.38 (1.65 to 3.12)	Ref.	2.06 (1.32 to 2.80)	Ref.	5.61 (4.88 to 6.33)	Ref.	31.32 (29.56 to 33.08)	Ref.	139.83 (135.42 to 144.23)	p <0.001
Incidence rate ratio (95% CI)	Ref.	2.19 (1.65 to 3.12)	Ref.	2.01 (1.53 to 2.67)	Ref.	1.61 (1.51 to 1.72)	Ref.	1.99 (1.91 to 2.08)	Ref.	2.58 (2.49 to 2.67)	p <0.001

CI: confidence interval; PY: person-years; Ref: reference

was no evidence for effect modification by age for all hospital outcomes of interest (p of interaction >0.05).

Predictors for mortality

Table 3 and 4 show baseline risk factors for in-hospital mortality during the first and second waves. Among the adjusted regression analysis, the main risk factors were the prevalence of chronic kidney disease stage 5 and/or hemodialysis (first wave: aOR 3.26 [95% CI: 2.47 to 4.31), p <0.001]; second wave: aOR 4.02 [95% CI: 3.31 to 4.89], p <0.001) and haematological malignancy (first wave: aOR 3.03 [95% CI: 1.97 to 4.66)], p <0.001; second wave: aOR 2.39 [95% CI: 1.92 to 2.98], p <0.001).

Discussion

This nationwide cohort study of hospitalised COVID-19 patients in Switzerland revealed several key findings: First, hospitalisation rates in patients with COVID-19 were highest among adults older than 50 years and more pronounced

Figure 2: Odds ratios and 95% confidence intervals for adverse outcomes in prespecified age subgroups. First wave was chosen as a reference. There was no evidence for effect modification by age for all hospital outcomes of interest (p of interaction >0.05). * adjusted for age, sex and Elixhauser comorbidity Index ARDS: acute respiratory distress syndrome; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; N/A: not applicable; no: number; OR: odds ratio

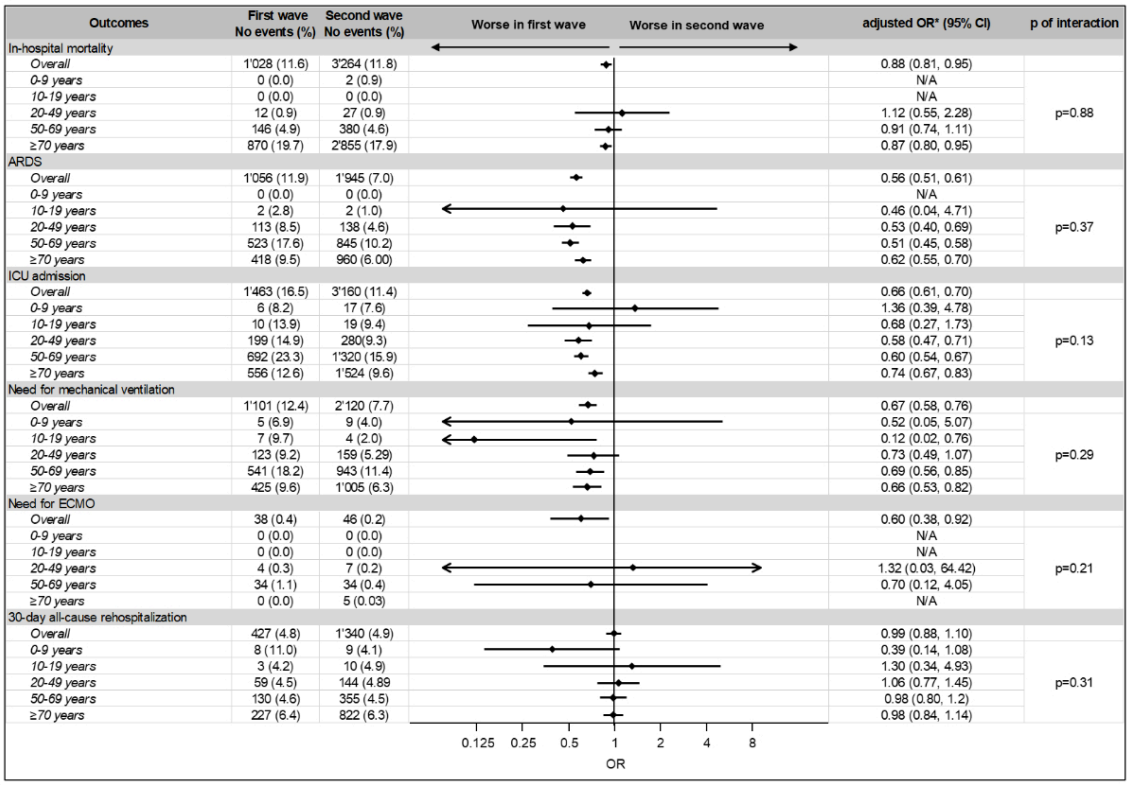
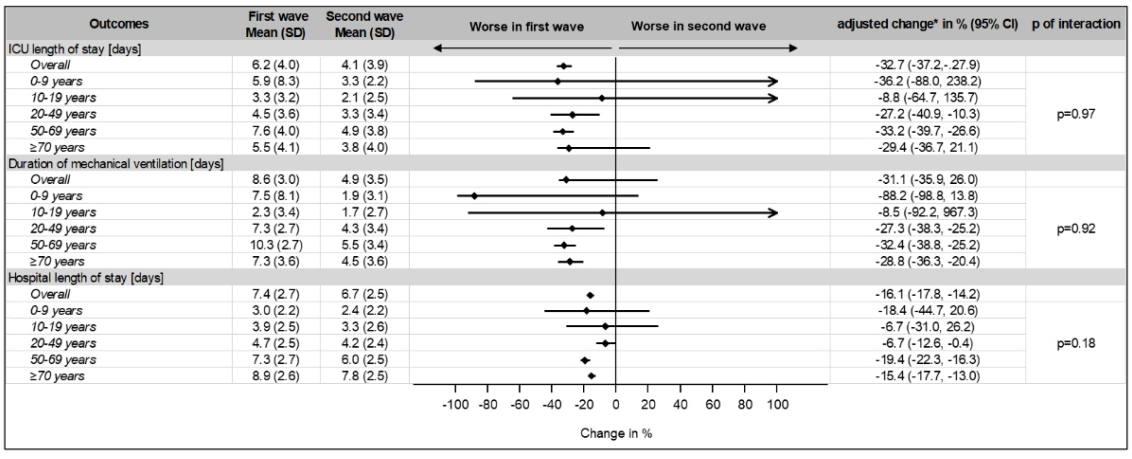


Figure 3: Changes in frequency for adverse outcomes in prespecified age subgroups. First wave was chosen as a reference. There was no evidence for effect modification by age for all hospital outcomes of interest (p of interaction >0.05). * adjusted for age, sex and Elixhauser comorbidity Index CI: confidence interval; ICU: intensive care unit; SD: standard deviation



during the second wave. Second, while the hospitalisation rate was higher among the overall Swiss population during the second wave, it was lower among positively tested individuals during the same period. Third, except for readmission, the risk for hospital-associated adverse outcomes was lower during the second wave, irrespective of patient age.

The highest hospitalisation rates among the overall Swiss population were observed in patients aged 50 years and older, both during the first and second wave. However, the peak of hospitalisations during the second wave was much higher than the first wave. These results are plausible since we observed significantly more infections during the second wave, resulting in more hospitalisations. Although data must be interpreted carefully, as hospitalisation and test criteria differed between the two waves, we observed a lower proportion of hospitalised people among the overall positively tested population during the second wave.

Improvement of patient management was a further important key component which was achieved during the second wave. Overall, the odds of adverse outcomes decreased during the second wave, except for hospital readmission. The expected decrease of in-hospital adverse events during the second wave is probably explained by the improved understanding of the treating physicians and nursing staff about the management of COVID-19 patients [18]. Importantly, the widespread administration of dexamethasone during the second wave may have contributed to a stronger reduction in in-hospital mortality, as already shown by previous studies [19]. Consistent with other studies [20–24], we observed a lower risk of in-hospital mortality during the second wave (aOR 0.88 [95% CI: 0.81 to 0.95]). While, as compared with findings from clinical trials, a relative risk reduction of 12% may seem small, hospitalised patients during the second wave tended to be older and more comorbid, both characteristics known to independently increase the risk of COVID-19-related mortality [25–28].

Similarly, corticosteroids may also have reduced the rate of progression to severe COVID-19 due to an attenuation of the inflammation, resulting in lower rates of ARDS, admission to ICU, need for mechanical ventilation and EC-

Table 3:
Risk factor analysis for in-hospital mortality during the first pandemic wave.

	Factor	Survivors (n = 7,834)	Non-survivors (n = 1,028)	Unadjusted OR (95% CI), p-value	Adjusted OR* (95% CI), p-value
Demographics	Age, median (IQR) [years]	67 (54,78)	81 (73,86)	1.07 (1.06, 1.08), **p <0.001**	1.07 (1.06, 1.08), **p <0.001**
	Male sex, n (%)	4493 (57.4)	700 (68.1)	1.59 (1.38, 1.82), **p <0.001**	1.96 (1.69, 2.28), **p <0.001**
	Swiss nationality, n (%)	5750 (73.4)	836 (81.3)	1.58 (1.34, 1.86), **p <0.001**	0.97 (0.81, 1.16), p = 0.728
	Supplementary insurance, n (%)	952 (12.2)	109 (10.6)	0.86 (0.70, 1.06), p = 0.151	0.74 (0.60, 0.93), **p = 0.008**
Admission data	Emergency admission, n (%)	6410 (81.8)	883 (85.9)	1.35 (1.12, 1.63), **p = 0.001**	1.68 (1.38, 2.04), **p <0.001**
	Admission from home, n (%)	5988 (76.4)	724 (70.4)	0.73 (0.64, 0.85), **p <0.001**	1.16 (1.00, 1.36), p = 0.054
	Admission to tertiary care hospital: University hospital, n (%)	2520 (32.2)	287 (27.9)	0.82 (0.71, 0.94), **p = 0.006**	0.84 (0.72, 0.98), **p = 0.027**
	Admission to tertiary care hospital: Non-university hospital, n (%)	3789 (48.5)	562 (54.7)	1.28 (1.12, 1.46), **p <0.001**	1.29 (1.12, 1.48), **p <0.001**
	Admission to secondary care hospital, n (%)	1516 (19.4)	179 (17.4)	0.88 (0.74, 1.04), p = 0.137	0.84 (0.70, 1.00), p = 0.055
Comorbidities, n (%)	Hypertension, n (%)	3437 (43.9)	579 (56.3)	1.65 (1.45, 1.88), **p <0.001**	0.67 (0.57, 0.78), **p <0.001**
	Dyslipidemia, n (%)	1256 (16.0)	178 (17.3)	1.10 (0.92, 1.30), p = 0.294	0.74 (0.61, 0.88), **p = 0.001**
	Obesity (BMI ≥30.0 kg/m^2), n (%)	241 (3.1)	34 (3.3)	1.08 (0.75, 1.55), p = 0.688	1.39 (0.94, 2.07), p = 0.100
	Coronary artery disease, n (%)	971 (12.4)	253 (24.6)	2.31 (1.97, 2.70), **p <0.001**	1.21 (1.02, 1.43), **p = 0.030**
	Atrial fibrillation, n (%)	1043 (13.3)	296 (28.8)	2.63 (2.27, 3.06), **p <0.001**	1.15 (0.97, 1.37), p = 0.104
	Congestive heart failure, n (%)	604 (7.7)	223 (21.7)	3.32 (2.80, 3.93), **p <0.001**	1.47 (1.21, 1.80), **p <0.001**
	Peripheral arterial disease, n (%)	210 (2.7)	56 (5.4)	2.09 (1.55, 2.83), **p <0.001**	0.89 (0.64, 1.23), p = 0.488
	Cerebrovascular disease, n (%)	305 (3.9)	81 (7.9)	2.11 (1.64, 2.72), **p <0.001**	1.35 (1.03, 1.77), **p = 0.029**
	Chronic obstructive pulmonary disease, n (%)	467 (6.0)	114 (11.1)	1.97 (1.59, 2.44), **p <0.001**	1.20 (0.95, 1.51), p = 0.132
	Bronchial asthma, n (%)	379 (4.8)	19 (1.8)	0.37 (0.23, 0.59), **p <0.001**	0.52 (0.32, 0.85), **p = 0.008**
	Obstructive sleep apnoea syndrome, n (%)	361 (4.6)	68 (6.6)	1.47 (1.12, 1.92), **p = 0.005**	1.37 (1.03, 1.83), **p = 0.029**
	Chronic kidney disease stage 3 & 4, n (%)	649 (8.3)	196 (19.1)	2.61 (2.19, 3.11), **p <0.001**	1.02 (0.84, 1.24), p = 0.851
	Chronic kidney disease stage 5 & hemodialysis, n (%)	212 (2.7)	93 (9.0)	3.58 (2.78, 4.61), **p <0.001**	3.26 (2.47, 4.31), **p <0.001**
	Solid organ transplant recipients, n (%)	65 (0.8)	8 (0.8)	0.94 (0.45, 1.96), p = 0.864	1.42 (0.65, 3.13), p = 0.389
	Solid tumor, n (%)	328 (4.2)	97 (9.4)	2.38 (1.88, 3.02), **p <0.001**	1.87 (1.44, 2.42), **p <0.001**
	Liver disease including cirrhosis, n (%)	427 (5.5)	85 (8.3)	1.56 (1.23, 1.99), **p <0.001**	1.86 (1.43, 2.42), **p <0.001**
	Diabetes mellitus type 2, n (%)	1447 (18.5)	265 (25.8)	1.53 (1.32, 1.78), **p <0.001**	0.97 (0.82, 1.15), p = 0.758
	Diabetes mellitus type 1, n (%)	27 (0.3)	4 (0.4)	1.13 (0.39, 3.23), p = 0.821	1.75 (0.56, 5.44), p = 0.335
	Haematological malignancy, n (%)	98 (1.3)	34 (3.3)	2.70 (1.82, 4.01), **p <0.001**	3.03 (1.97, 4.66), **p <0.001**
	Rheumatoid arthritis, n (%)	81 (1.0)	16 (1.6)	1.51 (0.88, 2.60), p = 0.133	1.45 (0.82, 2.56), p = 0.203
	Human immunodeficiency virus infection, n (%)	37 (0.5)	2 (0.2)	0.41 (0.10, 1.71), p = 0.221	0.67 (0.16, 2.91), p = 0.597
	Elixhauser comorbidity index, median (IQR)	2 (1, 4)	3 (2, 5)	1.27 (1.24, 1.31), **p <0.001**	1.13 (1.10, 1.17), **p <0.001**
Hospital frailty score	<5 points, n (%)	5061 (64.6)	449 (43.7)	0.42 (0.37, 0.48), **p <0.001**	0.92 (0.79, 1.08), p = 0.304
	5–15 points, n (%)	2377 (30.3)	507 (49.3)	2.23 (1.96, 2.55), **p <0.001**	1.22 (1.06, 1.41), **p = 0.006**
	>15 points, n (%)	396 (5.1)	72 (7.0)	1.41 (1.09, 1.83), **p = 0.009**	0.64 (0.49, 0.85), **p = 0.002**

* adjusted for age, sex and Elixhauser comorbidity Index

BMI: body mass index; IQR: interquartile range; OR: odds ratio

MO support as well as a 16% shorter LOS of 7.4 vs. 6.7 days [29]. In addition, the reduction in LOS during the second wave could also be due to improved discharge processes and earlier transfer to rehabilitation facilities. This was possible since many rehabilitation facilities were obligated to unburden acute care hospitals by accepting still-infectious COVID-19 patients [30].

We did not observe a change in readmission rates between the two waves. This can be explained by the fact that COVID-19 is an acute disease and may not lead to readmissions *per se*, whereas the burden of comorbidities as a potential driver for readmission tended to be higher during the second wave and may have diluted any beneficial effect on hospital readmission. These data must be interpreted in the context of the study design. As COVID-19 hospitalisations were identified using ICD-10-GM codes used for billing purposes, thus, misclassification and underreporting are possible, especially during the beginning of the pandemic when no specific ICD-10 codes were available. In line, the database provided by the FSO revealed larger numbers of hospitalisations as compared with data from the CH-SUR database. Since algorithms based on the U07.1 code had high sensitivity among hospitalised patients but at the expense of low specificity [31], it is likely that the number of hospitalisation with COVID-19 as provided by the FSO might be overestimated. However, it can also not be excluded that some hospitalisations with COVID-19 in the FSO-database were not lab-confirmed during the hospital stay but diagnosed based on an out-of-hospital test or clinical features. Second, unmeasurable confounding like smoking status, genetic susceptibility or home medication must be considered, as the used dataset does not include any information in this regard. Third, due to the study's retrospective design, no causal inference is possible. Fourth, we did not account for potential within-patient/hospital clustering. However, we do not think that accounting for clustering relevantly changes the conclusion of our manuscript, as the number of clusters (hospitals, hospital admissions per patient) were comparable between the first and second waves of the pandemic. Fifth, medical treatments received during the hospitalisation for COVID-19 could not be analysed, as this information is

Table 4:
Risk factor analysis for in-hospital mortality during the second pandemic wave.

Factor		Survivors (n = 24,391)	Non-Survivors (n = 3,264)	unadjusted OR (95% CI), p-value	adjusted OR* (95% CI), p-value
Demographics	Age, median (IQR) [years]	71 (58,81)	82 (75, 87)	1.07 (1.06, 1.07), **p <0.001**	1.07 (1.06, 1.07), **p <0.001**
	Male sex, n (%)	13,595 (55.7)	2123 (65.0)	1.48 (1.37, 1.59), **p <0.001**	1.79 (1.65, 1.94), **p <0.001**
	Swiss nationality, n (%)	18,069 (74.1)	2661 (81.5)	1.54 (1.41, 1.69), **p <0.001**	0.94 (0.85, 1.04), p = 0.238
	Supplementary insurance, n (%)	3448 (14.1)	531 (16.3)	1.18 (1.07, 1.30), **p = 0.001**	0.94 (0.85, 1.05), p = 0.310
Admission data	Emergency admission, n (%)	20,420 (83.7)	2822 (86.5)	1.24 (1.12, 1.38), **p <0.001**	1.48 (1.33, 1.66), **p <0.001**
	Admission from home, n (%)	19,609 (80.4)	2351 (72.0)	0.63 (0.58, 0.68), **p <0.001**	**0.91 (0.83, 0.99), p = 0.031**
	Admission to tertiary care hospital				
	University hospital, n (%)	5555 (22.8)	658 (20.2)	0.86 (0.78, 0.94), **p = 0.001**	0.92 (0.84, 1.01), p = 0.093
	Non-university hospital, n (%)	14,087 (57.8)	2025 (62.0)	1.20 (1.11, 1.29), **p <0.001**	1.16 (1.07, 1.25), **p <0.001**
	Admission to secondary care hospital, n (%)	4749 (19.5)	581 (17.8)	0.90 (0.81, 0.99), **p = 0.023**	0.87 (0.79, 0.96), **p = 0.006**
Comorbidities, n (%)	Hypertension, n (%)	11,700 (48.0)	1811 (55.5)	1.35 (1.26, 1.46), **p <0.001**	0.58 (0.53, 0.63), **p <0.001**
	Dyslipidemia, n (%)	4008 (16.4)	536 (16.4)	1.00 (0.91, 1.10), p = 0.998	0.69 (0.62, 0.76), **p <0.001**
	Obesity (BMI ≥ 30.0 kg/m2), n (%)	968 (4.0)	133 (4.1)	1.03 (0.85, 1.24), p = 0.771	1.08 (0.89, 1.33), p = 0.430
	Coronary artery disease, n (%)	3563 (14.6)	835 (25.6)	2.01 (1.84, 2.19), **p <0.001**	1.13 (1.03, 1.25), **p = 0.008**
	Atrial fibrillation, n (%)	3703 (15.2)	1079 (33.1)	2.76 (2.54, 3.00), **p <0.001**	1.27 (1.16, 1.39), **p <0.001**
	Congestive heart failure, n (%)	2050 (8.4)	772 (23.7)	3.38 (3.08, 3.70), **p <0.001**	1.63 (1.46, 1.81), **p <0.001**
	Peripheral arterial disease, n (%)	752 (3.1)	180 (5.5)	1.83 (1.55, 2.17), **p <0.001**	0.90 (0.75, 1.07), p = 0.224
	Cerebrovascular disease, n (%)	1015 (4.2)	235 (7.2)	1.79 (1.54, 2.07), **p <0.001**	1.11 (0.95, 1.30), p = 0.184
	Chronic obstructive pulmonary disease, n (%)	1528 (6.3)	379 (11.6)	1.97 (1.74, 2.21), **p <0.001**	1.26 (1.11, 1.43), **p <0.001**
	Bronchial asthma, n (%)	962 (3.9)	83 (2.5)	0.64 (0.51, 0.80), **p <0.001**	0.67 (0.53, 0.85), **p = 0.001**
	Obstructive sleep apnoea syndrome, n (%)	1068 (4.4)	158 (4.8)	1.11 (0.94, 1.32), p = 0.229	0.98 (0.82, 1.18), p = 0.870
	Chronic kidney disease stage 3 & 4, n (%)	2891 (11.9)	825 (25.3)	2.52 (2.30, 2.75), **p <0.001**	1.07 (0.97, 1.18), p = 0.201
	Chronic kidney disease stage 5 & hemodialysis, n (%)	328 (1.3)	200 (6.1)	4.79 (4.00, 5.73), **p <0.001**	4.02 (3.31, 4.89), **p <0.001**
	Solid organ transplant recipients, n (%)	252 (1.0)	27 (0.8)	0.80 (0.54, 1.19), p = 0.270	1.21 (0.80, 1.84), p = 0.368
	Solid tumor, n (%)	1201 (4.9)	326 (10.0)	2.14 (1.88, 2.44), **p <0.001**	1.61 (1.40, 1.85), **p <0.001**
	Liver disease including cirrhosis, n (%)	861 (3.5)	190 (5.8)	1.69 (1.44, 1.99), **p <0.001**	1.88 (1.57, 2.25), **p <0.001**
	Diabetes mellitus type 2, n (%)	5366 (22.0)	910 (27.9)	1.37 (1.26, 1.49), **p <0.001**	0.95 (0.87, 1.05), p = 0.321
	Diabetes mellitus type 1, n (%)	104 (0.4)	6 (0.2)	0.43 (0.19, 0.98), **p = 0.045**	0.61 (0.26, 1.43), p = 0.253
	Haematological malignancy, n (%)	402 (1.6)	124 (3.8)	2.36 (1.92, 2.89), **p <0.001**	2.39 (1.92, 2.98), **p <0.001**
	Rheumatoid arthritis, n (%)	324 (1.3)	57 (1.7)	1.32 (0.99, 1.75), p = 0.055	1.07 (0.80, 1.44), p = 0.655
	Human immunodeficiency virus infection, n (%)	98 (0.4)	4 (0.1)	0.30 (0.11, 0.83), **p = 0.020**	0.56 (0.20, 1.56), p = 0.271
	Elixhauser comorbidity index, median (IQR)	2 (1, 4)	3 (2, 5)	1.27 (1.25, 1.29), **p <0.001**	1.16 (1.14, 1.18), **p <0.001**
Hospital frailty score	<5 points, n (%)	15,645 (64.1)	449 (43.7)	0.36 (0.33, 0.39), **p <0.001**	0.70 (0.64, 0.76), **p <0.001**
	5–15 points, n (%)	7551 (31.0)	1686 (51.7)	2.38 (2.21, 2.57), **p <0.001**	1.40 (1.29, 1.51), **p = 0.006**
	>15 points, n (%)	1195 (4.9)	302 (9.3)	1.98 (1.73, 2.26), **p <0.001**	0.97 (0.84, 1.12), **p = 0.678**

* adjusted for age, sex and Elixhauser comorbidity Index.

BMI: body mass index; IQR: interquartile range; OR: odds ratio

missing in the analysed dataset. However, there are several strengths of note. This analysis was based on nationwide hospital care data with high external validity, strong statistical power and high generalisability across all regions in Switzerland. Moreover, this study provides insights into different age groups that were not comprehensively addressed in earlier studies in Switzerland.

Conclusion

In this nationwide cohort study, hospitalisation rates of COVID-19 patients were highest among adults older than 50 years and during the second wave. Except for readmission, the risk of hospital adverse outcomes was decreased during the second wave, regardless of the patient`s age.

Data sharing statement

The data supporting this study's findings are available upon request from the Swiss Federal Statistical Office (Neuchâtel, Switzerland). Restrictions apply to the availability of these data, which were used under license for this study. Data are available as part of the data on "Medizinische Statistik der Krankenhäuser" with the permission of the Swiss Federal Statistical Office, Section Health Services and Population Health.

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Potential conflicts of interest
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1:
ICD-10 codes for inclusion criteria.

Name	ICD-10 diagnosis code	Code position
COVID-19, virus confirmed	U071	Any
COVID-19, virus not confirmed	U072	Any

Table S2:
ICD-10 codes for baseline characteristics (comorbidities) and outcomes.

Name of group	ICD-10 diagnosis code	Code position: comorbidities
Hypertension	I10–I13, I15, I674	Any
Dyslipidemia	E78	Any
Obesity (BMI ≥ 30.0 kg/m2)	E65–E66	Any
Coronary artery disease	I20–I25	Any
Congestive heart failure	I50, I110, I130, I132	Any
Peripheral arterial disease	I702	Any
Cerebrovascular disease	I60–I67, I69	Any
Chronic obstructive pulmonary disease	J44	Any
Bronchial asthma	J45–J46	Any
Obstructive sleep apnoea syndrome	G473	Any
Acute respiratory distress syndrome	J80	Any
Chronic kidney disease stage 3 & 4	N183–N184	Any
Chronic kidney disease stage 5 & hemodialysis	N185, T824, T8571,Z491–Z492, Z992	Any
Solid organ transplant recipients	T861–T864, T8681–T8682, T8688, T869, Z940–Z944, Z9488, Z949	Any
Solid tumor	C0–C7	Any
Liver disease including cirrhosis	K7, K703, K717, K744, K746 K7470–K7472	Any
Diabetes mellitus type 1	E10	Any
Diabetes mellitus type 2	E11	Any
Haematological malignancy	C81–88, C90–C96)	Any
Rheumatoid arthritis	M05–M06, M08	Any
Human immunodeficiency virus infection	B20–B24, F024, O987, U60–U61, U85, Z21	Any

Table S3:
CHOP codes baseline characteristics (comorbidities) and outcomes.

Name	CHOP code	Code position
Haemo- and peritoneal dialysis	3895, 3927, 3942–3943, 39951–39954, 3995I1–3995I2, 5498	Any
Solid organ transplant	0091*–0093*,335*–336*, 3751*,4194*,4697*,505*,528*,556*	Any
Installation and revision of portosystemic shunt	391100, 391199	Any
Extracorporeal membrane oxygenation	37698*, 3769A*, 376A61*– 376A62*, 376A71*–376A73*, 376B61*– 376B62*, 376B71*–376B73*, 376C61*, 376C62*, 376C71*–376C73*, 376D*, 376D31*, 376D41*	Any

Table S4:
Baseline characteristics stratified by waves.

		First wave	Second wave	p-value
Hospitalisations, n		8862	27,655	
Demographics	Age, median (IQR) [years]	69 (55, 80)	73 (60, 82)	<0.001
	Age groups, n (%)			
	<10 years	73 (0.8)	224 (0.8)	<0.001
	10–19 years	72 (0.8)	203 (0.7)	
	20–49 years	1333 (15.0)	3005 (10.9)	
	50–69 years	2974 (33.6)	8304 (30.0)	
	≥70 years	4410 (49.8)	15,919 (57.6)	
	Male sex, n (%)	5,193 (58.6)	15,718 (56.8)	0.004
	Swiss nationality, n (%)	6586 (74.3)	20,730 (75.0)	0.23
	Supplementary insurance, n (%)	1061 (12.0)	3979 (14.4)	<0.001
Admission data	Emergency admission, n (%)	7293 (82.3)	23,242 (84.0)	<0.001
	Admission from home, n (%)	6712 (75.7)	21,960 (79.4)	<0.001
	Admission to tertiary care hospital, n (%)			<0.001
	University hospital	2807 (31.7)	6213 (22.5)	
	Non-university hospital	4360 (49.2)	16,112 (58.3)	
	Admission to secondary care hospital, n (%)	1695 (19.1)	5330 (19.3)	
Comorbidities, n (%)	Hypertension	4016 (45.3)	13,511 (48.9)	<0.001
	Dyslipidemia	1434 (16.2)	4544 (16.4)	0.58
	Obesity (BMI ≥ 30.0 kg/m2)	275 (3.1)	1101 (4.0)	<0.001
	Coronary artery disease	1224 (13.8)	4398 (15.9)	<0.001
	Atrial fibrillation	1339 (15.1)	4782 (17.3)	<0.001
	Congestive heart failure	827 (9.3)	2822 (10.2)	0.017
	Peripheral arterial disease	266 (3.0)	932 (3.4)	0.090
	Cerebrovascular disease	386 (4.4)	1250 (4.5)	0.52
	Chronic obstructive pulmonary disease	581 (6.6)	1907 (6.9)	0.27
	Bronchial asthma	398 (4.5)	1,045 (3.8)	0.003
	Obstructive sleep apnea syndrome	429 (4.8)	1226 (4.4)	0.11
	Chronic kidney disease stage 3 & 4	845 (9.5)	3716 (13.4)	<0.001
	Chronic kidney disease stage 5 & hemodialysis	305 (3.4)	528 (1.9)	<0.001
	Solid organ transplant recipients	73 (0.8)	279 (1.0)	0.12
	Solid tumor	425 (4.8)	1527 (5.5)	0.008
	Liver disease including cirrhosis	512 (5.8)	1051 (3.8)	<0.001
	Diabetes mellitus type 2	1712 (19.3)	6276 (22.7)	<0.001
	Diabetes mellitus type 1	31 (0.3)	110 (0.4)	0.53
	Haematological malignancy	132 (1.5)	526 (1.9)	0.011
	Rheumatoid arthritis	97 (1.1)	381 (1.4)	0.041
	Human immunodeficiency virus infection	39 (0.4)	102 (0.4)	0.35
	Elixhauser comorbidity index, median (IQR)	2 (1, 4)	2 (1, 4)	<0.001
Hospital frailty score, n (%)	<5 points	5510 (62.2)	16,921 (61.2)	0.25
	5–15 points	2884 (32.5)	9237 (33.4)	
	>15 points	468 (5.3)	1497 (5.4)	
Outcomes	In-hospital mortality, n (%)	1028 (11.6)	3264 (11.8)	0.61
	ICU admissions, n (%)	1463 (16.5)	3160 (11.4)	<0.001
	ICU LOS, median (IQR) [days]	8.3(2.1, 18.3)	4.9 (1.8, 11.7)	<0.001
	Need for mechanical ventilation, n (%)	1101 (12.4)	2120 (7.7)	<0.001
	Duration of mechanical ventilation, median (IQR) [days]	10.7 (5.0, 18.3)	6.3 (2.0, 13.0)	<0.001
	30-days rehospitalisation, n (%)	427 (4.8)	1340 (4.8)	0.92

BMI: body mass index; ICU: intensive care unit; IQR: interquartile range; LOS: length of hospital stay.