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Comparison of characteristics, predictors and outcomes between the first and second COVID-19 waves in a tertiary care centre in Switzerland: an observational analysis

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Summary

AIM OF THE STUDY: To compare admission characteristics, predictors and outcomes of patients with confirmed coronavirus disease 2019 (COVID-19) hospitalised in a tertiary care hospital in Switzerland during the first and second waves of the pandemic.

METHODS: This retrospective observational analysis included adult patients with severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection confirmed by a real-time reverse transcriptase polymerase chain reaction (RT-PCR) or rapid antigen test and hospitalised at the Cantonal Hospital Aarau from 26 February to 30 April 2020 (first wave) and from 1 October to 31 December 2020 (second wave). The primary endpoint was all-cause in-hospital mortality. The secondary endpoints were transfer to the intensive care unit (ICU) and length of hospital stay (LOS).

RESULTS: Overall, 486 patients (mean age 65.9 years ± 14.7 SD, 65% male) were included. Ninety-two patients (19%) died during the hospital stay and 92 patients (19%) were transferred to the ICU. Admission characteristics, including comorbidities and frailty, were similar for patients of the first (n = 100) and second wave (n = 386). However, during the second wave the median time from symptom onset to presentation to the emergency department (ED) was shorter (7 days, interquartile range [IQR] 4–9 vs 8 days, IQR 4–11; p = 0.02). In the second wave, most patients received high-dose glucocorticoid treatment (0% vs 76%, p <0.01). In-hospital mortality was similar among COVID-19 patients in the first (19/100, 19%) and second wave (73/386, 19%); this finding persisted after full adjustment in multiple regression models (adjusted odds ratio [aOR] 1.18, 95% confidence interval [CI] 0.49–2.80; p = 0.71). Risk for ICU admission was also similar (24% vs 18%; aOR 0.98, 95% CI 0.46–2.06; p = 0.95). More patients were transferred to rehabilitation facilities in the second wave (18% vs 31%; aOR 2.06, 95% CI 1.04–4.07; p = 0.04) and LOS was 2.5 days shorter (9.0 vs 6.5 days; adjusted difference −2.53 days, 95%-CI −4.51 to −0.54; p = 0.01). Main predictors for in-hospital death were patient age (aOR 1.07, 95% CI 1.02–1.11; p <0.01), male sex (aOR 2.41, 95% CI 1.05–5.55; p = 0.04) and the age-adjusted Charlson comorbidity index (aOR 1.27, 95% CI 1.09–1.48 p <0.01).

CONCLUSION: Despite differing treatment regimens, mortality and ICU admission remained largely unchanged for COVID-19 patients admitted during the second wave of the pandemic in our tertiary care hospital. However, discharge processes were optimised with patients leaving the hospital earlier and going to rehabilitation facilities more often.

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Introduction

The emergence and subsequent spread of the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) still has a major detrimental impact on healthcare systems worldwide. Today, over a year after its first description in China [1, 2], the number of patients suffering from SARS-CoV-2 is still rising [3, 4]. After an initial wave in spring 2020, the number of new infections in Switzerland and other European countries plateaued over the summer months [3, 5]. With the arrival of autumn, however, infection rates rose again and eventually surpassed the numbers of the first wave [3, 6].

The severe and highly contagious coronavirus disease 2019 (COVID-19) led to an enormous global effort aiming to reduce infection rates. There has also been a major endeavour to improve therapeutic management and thus clinical outcomes and COVID-19 associated mortality. Nev-

ertheless, evidence-based treatment options are currently limited to early anti-coagulation, glucocorticoid use, oxygen administration and different supportive treatments; other experimental treatments have shown mixed results [7–13]. Increasing clinical experience and the more widespread use of high-dose glucocorticoids in patients with COVID-19 pneumonitis might have led to improved clinical courses of patients in the second wave, as well as improvements in the general management of in-hospital patients and a reduction in length of stay (LOS).

Whereas several studies reported characteristics and outcomes of patients with COVID-19 during the early pandemic, including a report from our hospital [14], only a few anticipatory [15, 16] and early second-wave publications are already available. These focus, for example, on changes in treatment regimens [10, 13], triage [17] or epidemiological data [18]. More recently, cohort data on hospitalised Swiss patients up to the end of August 2020 were published [19], and another group of authors reported a more severe second wave for member states of the African Union [20]. Potential differences between the two waves in Europe regarding outcomes have thus gone largely underreported. Hence, the aim of this study was to compare characteristics, predictors and outcomes of patients with COVID-19 hospitalised at a tertiary care centre in the northern part of Switzerland during the first and second waves of infection [14].

Methods

Study design and participants

This retrospective observational analysis included all consecutively hospitalised adult patients (≥18 years) with a confirmed SARS-CoV-2 infection and a LOS of at least 24 hours at the Cantonal Hospital Aarau (Switzerland) between 26 February and 30 April 2020 (first wave) and between 1 October and 31 December 2020 (second wave). In this tertiary care centre with 130 medical ward beds, indications for in-hospital treatment of COVID-19 were respiratory distress with need for oxygen supplementation, high fever or relevant clinical deterioration. This study was approved by the local ethics committee (EKZN, 2020-01306).

A detailed description of the study methodology has been previously reported [14]. A confirmed SARS-CoV-2 infection was defined as a combination of typical clinical symptoms (e.g., respiratory symptoms with or without fever, and/or pulmonary infiltrates and/or anosmia/dysgeusia) and a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) test, obtained from nasopharyngeal swabs or lower respiratory tract samples, according to WHO guidance [8, 21]. During the second wave, more a- or oligosymptomatic patients with positive RT-PCR tests were hospitalised for non-COVID-19 reasons such as childbirth or trauma. In November 2020, rapid antigen testing was authorised by the Federal Office of Public Health in Switzerland. Hence, data for the second wave also include patients with positive rapid antigen tests. However, because of the lower predictive value for asymptomatic cases, we excluded patients without symptoms unless their rapid antigen results were confirmed by a positive RT-PCR test. We further excluded patients from the analysis if they did not provide general informed consent or if they had not yet been discharged when data collection was closed (20 January 2021).

Data collection

All analysed data were collected as part of the clinical routine during the hospitalisation (from admission to discharge/death). We performed chart reviews and automatic export from the electronic health record (EHR), including vital signs and clinical characteristics upon admission, as well as sociodemographic factors, comorbidities based on pre-existing diagnoses and home medication. COVID-19-specific inpatient medication was assessed up to hospital discharge or death and exported from the EHR. Experimental treatment was offered to all suitable patients according to ongoing clinical trials and WHO guidelines [7, 8, 21]. The age-adjusted Charlson comorbidity index (ACCI) [22] and the Clinical Frailty Scale score (CFS) [23] were calculated for all patients as part of the clinical routine or through chart review. Laboratory values were available according to clinical routine and correspond to the first blood draw obtained within 24 hours from admission.

Definition of endpoints

The primary endpoint was defined as all-cause in-hospital mortality. The secondary endpoints were admission to the intensive care unit (ICU), discharge to a rehabilitation facility and length of hospital stay (LOS). All endpoints were verified through chart review.

Statistical analysis

Discrete variables are expressed as frequency (percentage) and continuous variables as medians with interquartile ranges (IQR) for skewed data, or mean with standard deviation (SD, for normally distributed data. We used the Wilcoxon rank-sum test to compare continuous variables and the Pearson's chi-square test to compare categorical or binary variables. We investigated the association of baseline risk factors with the primary and secondary endpoints by performing logistic regression for binary dependent variables and ordinary least-squares linear regression for continuous variables. Odds ratios (ORs) and regression coefficients were calculated with corresponding 95% confidence intervals (CIs), with p-values as measures of association and p_i-values as measures of interaction. We calculated three models. The first model was unadjusted (model 0). The second (model 1) was adjusted for sex, ACCI, CFS and immunomodulating home medication and the fully adjusted model 2 was further adjusted for time from symptom onset to admission and transfer from other hospitals. We also investigated subgroups of age, sex, ACCI and CFS, as well as ICU admission as sensitivity analyses. Overall model probability for adjusted ORs (aOR) was evaluated based on likelihood ratio chi-square tests and p-values for individual factors were derived from Wald tests. We considered a two-sided p-value of <0.05 significant and calculated the unadjusted area under the receiver operating characteristic curve (AUC) as a measure of discrimination. Statistical analysis was performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

Figure 1 provides an overview of the study flow and table 1 shows overall patient demographics, comorbidities and vital signs on admission, as well as stratified according to the first and the second wave. In total, 486 patients hospitalised with a confirmed SARS-CoV-2 infection were included in this analysis (mean age 65.9 years ± 14.7 SD, 65% male). Patients had a medium burden of comorbidities with a median ACCI of 3 points, indicating an estimated 10-year survival of 77% [22], and a median CFS of 3 points, suggesting well-controlled medical problems [23]. Hypertension was the most common comorbidity, affecting 282 patients (58%), followed by obesity (n = 142, 30%), diabetes (n = 141, 29%) and chronic kidney disease (n = 106, 22%).

Overall, admission characteristics for patients in the first wave (n = 100) and the second wave (n = 386) did not differ considerably. However, during the second wave, median time of symptom onset to presentation to the ED was significantly shorter (8 days, IQR 4–11 vs 7 days, IQR 4–9; p = 0.02). Patients were generally tachypnoeic, with a mean respiratory rate of 21/min ± 8 SD, indicating high clinical severity. No other significant difference in clinical presentation was found between the first and the second wave.

Treatment regimens, on the other hand, were markedly different. During the first wave, both antiviral (n = 40, 10% vs n = 46, 46%; p <0.01) and antibiotic treatment (n = 73, 19% vs n = 41, 41%; p <0.01) were more common than during the second. Furthermore, hydroxychloroquine (n = 43, 43%) was used only during the first wave and remdesivir (n =3 3, 8.6%) and high-dose glucocorticoids (n = 293, 76%) exclusively during the second. Invasive ventilation was also noticeably less common during the second wave (n = 19, 19.0% vs n = 46, 11.9%; p = 0.06).

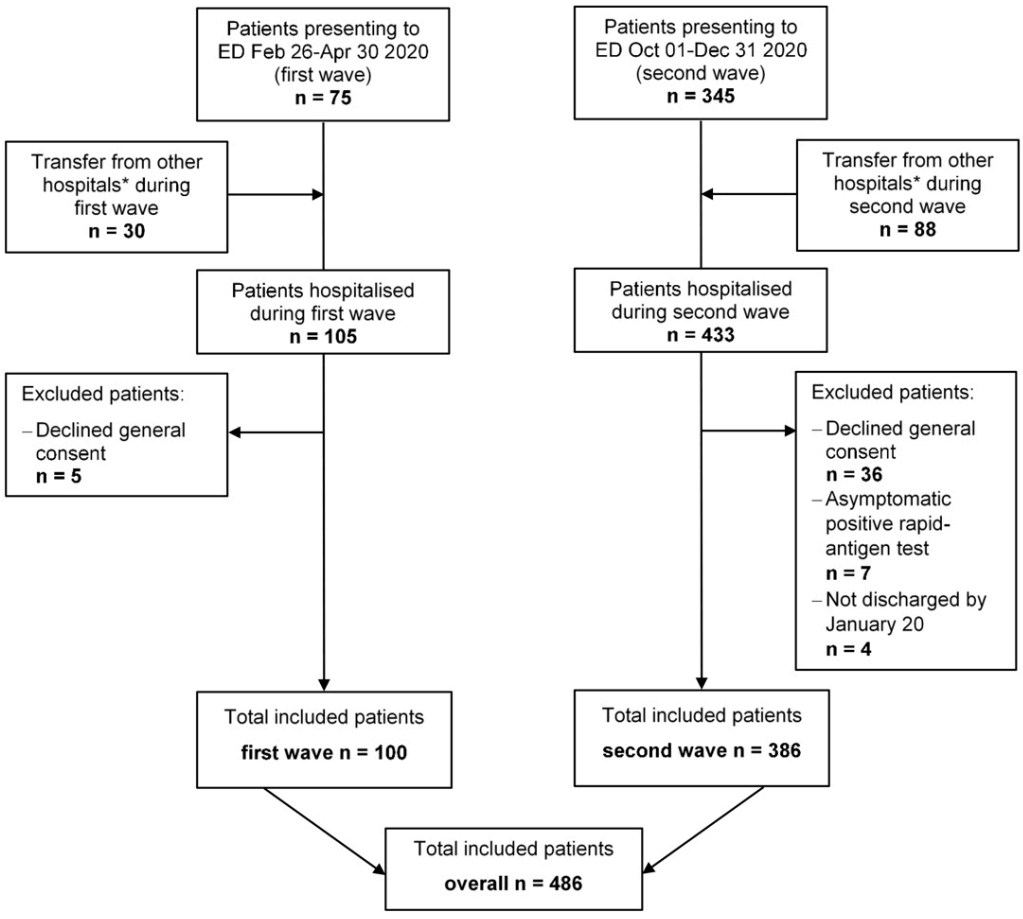
Comparison of outcomes between waves

Table 2 provides an overview of patient outcomes. A more detailed version can be found in the appendix (table S1). Overall, in-hospital death occurred in 92 patients (19%) and 92 patients (19%) were admitted to the ICU. After a median LOS of 7 days (IQR 4–13), most patients were discharged to home (n = 185, 38%) or rehabilitation care (n = 137, 28%).

In-hospital mortality was similar during the first (19/100, 19%) and second waves (73/386, 19%), which was confirmed in the adjusted regression analysis (adjusted OR [aOR] 1.18, 95% CI 0.49–2.80; p = 0.71).

Risk of ICU admission in the first and second wave was similar (24% vs 18%, aOR 0.98, 95% CI 0.46–2.06; p = 0.95). There were more transfers to rehabilitation facilities in the second wave (18% vs 31%, aOR 2.06, 95% CI 1.04–4.07; p = 0.04) and LOS was 2.5 days shorter (9 vs

Figure 1: Overview of study flow. A total of 486 patients were included in the final analysis. ED = emergency department * includes psychiatric and rehabilitation care hospitals.



6.5 days, adjusted difference −2.53 days, 95% CI −4.51 to −0.54; p = 0.01).

Subgroup analysis

Figure 2 illustrates the subgroup analysis for the primary endpoint. Though the overall aOR for wave suggests a trend toward the second wave (1.18, 95% CI 0.49–2.80; p = 0.71), the results were not significant. Similarly, none of the analysed subgroups provided evidence for effect modification between variables.

The subgroup analysis for ICU admission is summarised in figure 3. Overall, there was no significant difference between waves (aOR 0.98, 95% CI 0.46–2.06; p = 0.95). The results suggest, however, that women (aOR 0.32, 95% CI 0.06–1.71; p = 0.18) and patients with a higher frailty score (CFS ≥4: aOR 0.19, 95% CI 0.03–1.42; p = 0.11) were less often admitted to the ICU during the second wave. Again, effect modifications were not significant.

Sensitivity analysis

We performed a sensitivity analysis with stratification of patients based on frailty (CFS cut-off value of ≤3 points) in order to understand whether mortality differed between waves among patients who potentially qualified for intensive care treatment. We found no statistically significant difference in mortality for patients with a low frailty score (n = 7, 14% vs n = 19, 9%; p = 0.31; aOR 0.77. 95% CI 0.23–2.55; p = 0.66).

Predictors for mortality and ICU admission

The overview in table 3 shows association and predictive accuracy of baseline characteristics for in-hospital mortali-

Table 1: Baseline characteristics and treatment of patients hospitalised with confirmed SARS-CoV-2 infection.

Factor	Overall (n = 486)	First wave (n = 100)	Second wave (n = 386)	p-value*
Pre-admission history				
Age (years), mean ± SD	65.9 ± 14.7	65.8 ± 14.7	66.0 ± 14.8	0.90
Age ≥ 65 years, n (%)	276 (56.8%)	54 (54.0%)	222 (57.3%)	0.53
Sex, male, n (%)	317 (65.2%)	64 (64.0%)	253 (65.5%)	0.77
Nationality, Swiss, n (%)	272 (56.0%)	61 (61.0%)	211 (54.7%)	0.26
Transfer from other hospital, n (%)	110 (22.6%)	29 (29.0%)	81 (21.0%)	0.09
Time from symptom onset to admission (days), median (IQR)	7.0 (4.0–9.0)	8.0 (4.0–11.0)	7.0 (4.0–9.0)	**0.02**
Pre-existing home medication, n (%)	406 (83.7%)	80 (80.0%)	326 (84.7%)	0.26
– Immunomodulating medication, n (%)	44 (9.1%)	5 (5.0%)	39 (10.1%)	0.11
Presentation to emergency department				
Supplemental oxygen administered n (%)	111 (22.8%)	27 (27.0%)	84 (21.8%)	0.27
FiO_2 (%), mean ± SD	64.3 ± 28.4	56.4 ± 26.8	66.8 ± 28.5	0.10
Heart rate (bpm), mean ± SD	90 ± 18	87± 15	91 ± 19	0.09
Respiratory rate (rpm), mean ± SD	21 ± 8	21 ± 8	21 ± 8	0.67
Temperature (°C), mean ± SD	37.6 ± 1.0	37.8 ± 0.8	37.6 ± 1.0	0.30
Comorbidities				
ACCI, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–6.0)	3.0 (2.0–5.0)	0.36
ACCI ≥4 points, n (%)	232 (47.7%)	45 (45.0%)	187 (48.4%)	0.54
CFS, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.41
CFS ≥4 points, n (%)	173 (35.6%)	29 (29.0%)	144 (37.3%)	0.12
Smoker, n (%)	40 (12.2%)	7 (9.2%)	33 (13.1%)	0.36
Obesity (BMI >30 kg/m^2), n (%)	142 (30.2%)	27 (27.0%)	115 (31.1%)	0.43
Diabetes mellitus, n (%)	141 (29.0%)	22 (22.0%)	119 (30.8%)	0.08
Hypertension, n (%)	282 (58.0%)	57 (57.0%)	225 (58.3%)	0.82
Coronary artery disease, n (%)	93 (19.1%)	25 (25.0%)	68 (17.6%)	0.09
Chronic heart failure (LVEF<40%), n (%)	14 (2.9%)	3 (3.0%)	11 (2.9%)	0.94
Bronchial asthma, n (%)	29 (6.0%)	16 (16.0%)	13 (3.4%)	**<0.01**
COPD, n (%)	35 (7.2%)	7 (7.0%)	28 (7.3%)	0.93
OSAS, n (%)	46 (9.5%)	14 (14.0%)	32 (8.3%)	0.08
Solid organ transplant, n (%)	10 (2.1%)	1 (1.0%)	9 (2.3%)	0.40
Active rheumatic disease, n (%)	13 (2.7%)	2 (2.0%)	11 (2.8%)	0.64
Cancer	57 (11.7%)	11 (11.0%)	46 (11.9%)	0.80
Liver cirrhosis, n (%)	4 (0.8%)	0 (0.0%)	4 (1.0%)	0.31
Chronic kidney disease, n (%)	106 (21.8%)	28 (28.0%)	78 (20.2%)	0.09
SARS-CoV-2 infection treatment				
Experimental (antiviral) treatment	86 (17.7%)	46 (46.0%)	40 (10.4%)	**<0.01**
– Hydroxychloroquine†	43 (8.9%)	43 (43%)	0 (0.0%)	n.a.
– Remdesivir†	33 (6.8%)	0 (0.0%)	33 (8.6%)	n.a.
Antibiotic treatment	114 (23.5%)	41 (41.0%)	73 (18.9%)	**<0.01**
High-dose glucocorticoids	293 (60.4%)	0 (0.0%)	293 (76.1%)	**<0.01**

ACCI = age-adjusted Charlson comorbidity index; BMI = body mass index; bpm = beats per minute; CFS = clinical frailty scale; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; LVEF = left ventricular ejection fraction; n.a. = not applicable; OSAS = obstructive sleep apnoea syndrome; rpm = respirations per minute; SARS-CoV-2 = severe acute respiratory syndrome coronavirus type 2; SD = standard deviation Bold values denote statistical significance at the p≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables † Alone or in combination with other medication

ty, as indicated by their aOR and AUC values respectively. A more detailed table can be found in the appendix (table S2). Overall, non-survivors were older (mean 74.2 years ± 9.8 SD vs 64 years ± 15.0 SD; p <0.01), more often male (n = 68, 74% vs n = 249, 63%; p = 0.05) and had a higher burden of comorbidities (ACCI median 5, IQR 4–7 vs 3, IQR 2–5; p <0.01). Likewise, patients who died scored higher on the CFS than survivors (median 4, IQR 4–6 vs 3, IQR 2–4; p <0.01). They were also more likely to receive supplemental oxygen upon presentation (n = 45, 49% vs n = 66, 17%; p <0.01). Regression model 2 revealed a positive association of in-hospital death with all of the aforementioned factors, with the highest association for age ≥65 years (aOR 4.47, 95% CI 1.63–12.26; p <0.01) and supplemental oxygen (aOR 7.32, 95% CI 3.27–16.38; p <0.01).

The predictive accuracy of these factors ranged from moderate to high, especially age (AUC 0.71, 95% CI 0.66–0.76) and ACCI (AUC 0.73, 95% CI 0.69–0.78). Interestingly, male sex showed low prognostic value (AUC 0.55, 95% CI 0.50–0.60) and was not significantly associated with in-hospital mortality at all when we looked at only second wave patients (data not shown).

Table 2: Outcomes overall and stratified by wave. Odds ratios and regression coefficients for wave (base = first wave).

	Overall (n = 486)	First wave (n = 100)	Second Wave	p-value*	aOR/coefficient† (95% CI), p-value *Model 2*	
All-cause in-hospital mortality, n (%)	92 (18.9%)	19 (19.0%)	73 (18.9%)	0.98	aOR	1.18 (0.49 to 2.80), 0.71
Time to death (days), median (IQR)	10.0 (4.0–19.0)	15.0 (5.0–24.0)	9.0 (4.0–17.0)	0.07	Coefficient	−0.68† (−6.14 to 4.77), 0.80
ICU admission, n (%)	92 (18.9%)	24 (24.0%)	68 (17.6%)	0.15	aOR	0.98 (0.46 to 2.06), 0.95
Time to ICU (days), median (IQR)	1.0 (0.0–3.0)	0.5 (0.0–3.0)	1.0 (0.0–4.0)	0.70	Coefficient	−0.10† (−2.12 to 1.92), 0.92
ICU LOS (days), median (IQR)	9.0 (4.0–15.0)	9.0 (4.0–19.0)	9.0 (4.0–14.0)	0.59	Coefficient	−1.78† (−6.45 to 2.89), 0.45
Invasive ventilation, n (%)	65 (13.4%)	19 (19.0%)	46 (11.9%)	0.06	aOR	0.73 (0.33 to 1.64), 0.44
Hospital LOS (days), median (IQR)	7.0 (4.0–13.0)	9.0 (4.5–15.0)	6.5 (3.0–13.0)	**0.03**	Coefficient	**−2.53† (−4.51 to −0.54), 0.01**
Discharge status‡						
– Home care, n (%)	185 (38.1%)	47 (47.0%)	138 (35.8%)	**0.04**	aOR	0.55 (0.29 to 1.03), 0.06
– Rehabilitation care, (n (%)	137 (28.2%)	18 (18.0%)	119 (30.8%)	**0.01**	aOR	**2.06 (1.04 to 4.07), 0.04**
– Other hospital, n (%)	51 (10.5%)	16 (16.0%)	35 (9.1%)	**0.04**	aOR	0.58 (0.24 to 1.37), 0.21
– Nursing facility	20 (4.1%)	0 (0.0%)	20 (5.2%)	**0.02**	n.a.	
– Unknown	1 (0.2%)	0 (0.0%)	1 (0.3%)	0.61	n.a.	

ACCI = age-adjusted Charlson comorbidity index; aOR = adjusted odds ratio; CFS = clinical frailty scale; CI = confidence interval; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; n.a. = not applicable Bold values denote statistical significance at the p ≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables † Regression coefficients for continuous dependent variables ‡ Other than death Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital.

Figure 2: Subgroup analysis for all-cause in-hospital mortality. Fully adjusted OR (Model 2) for wave (base = first wave). Higher ACCI/CFS scores indicate higher burden of comorbidity/frailty. Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital.

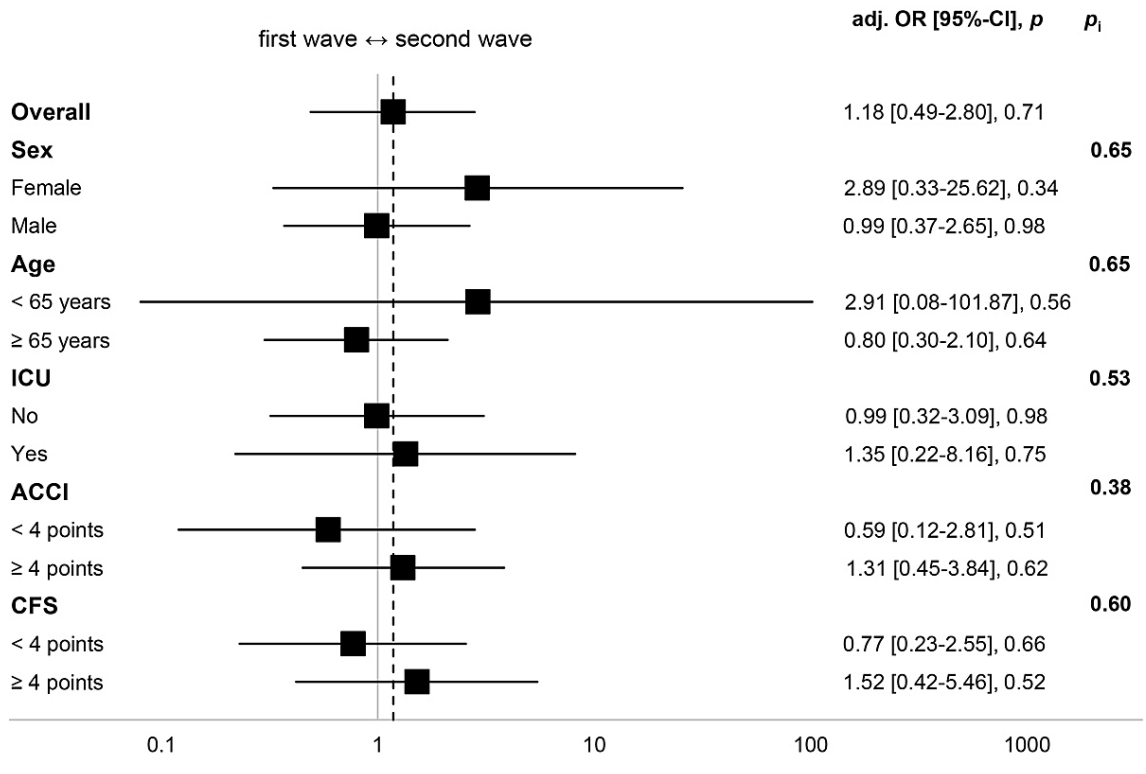


Table 4 shows association and discrimination results for baseline characteristics and ICU admission. A more detailed table can be found in the appendix (table S3). Patients admitted to the ICU were younger (mean 63.2 years ± 11.0 SD vs 66.6 years ± 15.4 SD, p = 0.05), more often male (n = 72, 78% vs n = 245, 62%; p <0.01) and admitted from other hospitals more often (n = 42, 46% vs n = 68, 17%; p <0.01). Although the burden of comorbidities and frailty were generally lower, patients admitted to the ICU were more often obese (BMI >30 kg/m^2 n = 34, 40% vs n = 108, 28%; p = 0.03). After full adjustment (model 2), transfer from another hospital (aOR 4.33, 95% CI 2.21–8.48; p <0.01) and oxygen supplementation (aOR 6.14, 95% CI 3.02–12.49; p <0.01) showed the highest association. Significant negative association was found for frailty (CFS aOR 0.66, 95% CI 0.46–0.93; p = 0.02) and immunomodulating home medication (aOR 0.66, 95% CI 0.46–0.92; p = 0.02).

Predictive accuracy of the analysed factors for ICU admission varied considerably, with FiO_2 (AUC 0.75, 95% CI 0.660.84), administration of supplemental oxygen in the ED (AUC 0.69, 95% CI 0.63–0.74) and the CFS (AUC 0.34, 95% CI 0.28–0.40) yielding the strongest results.

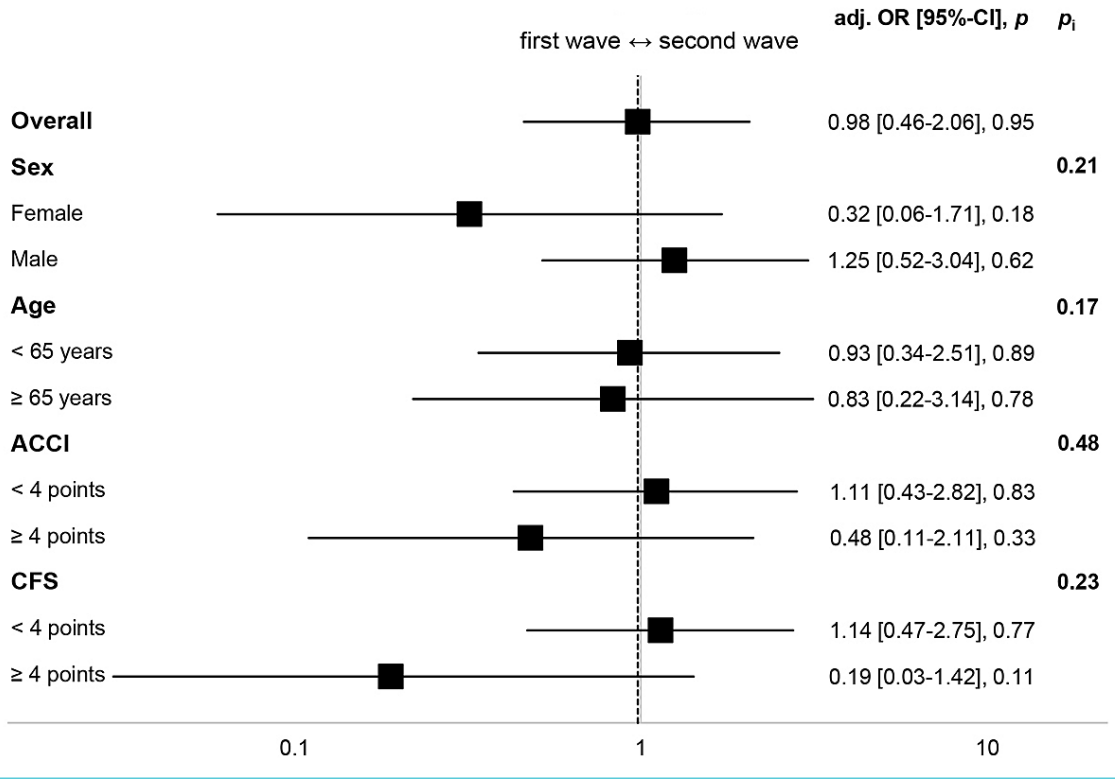
Discussion

To our knowledge, this study offers one of the first comparisons of consecutively hospitalised COVID-19 patients during the first and second waves of SARS-CoV-2 cases in Switzerland. Our results indicate only minor differences in clinical presentation, mortality and ICU admission, despite differing treatment regimens. However, LOS was 2.5 days shorter and patients were more likely to be discharged to rehabilitation care during the second wave.

The similarity of outcomes was surprising, as we had anticipated a reduction in mortality risks due to the increased experience regarding medical and supportive handling of COVID-19 patients and the more wide-spread use of high-dose glucocorticoids, which has been associated with lower mortality [11]. It is worth noting, though, that in a sensitivity analysis patients with a low frailty score, who potentially qualified for intensive care treatment, had a lower numerical mortality risk in the second wave, which, however, was not statistically significant. Clearly, our monocentric analysis was limited by a small sample size and patient selection regarding in-hospital treatment was potentially biased. For example, as a tertiary care centre, deteriorating patients were transferred to our institution if they were in need of more intensive treatment and milder cases were sent to peripheral hospitals, especially when fewer beds were available. In contrast, we discharged patients with milder symptoms to peripheral hospitals, leading to higher mortality rates in our hospital compared with those previously reported for other Swiss hospitals (19% vs 15%) [19].

Interestingly, figures from the Swiss Federal Office of Public Health show that overall mortality per 100,000 inhabitants has markedly changed between the waves in Switzerland, with a higher rate during the second wave [6]. However, for the canton of Aargau, where our hospital is situated, there was little difference between waves, which is reflected in our own results. Because epidemiological

Figure 3: Subgroup analysis for ICU admission. Fully adjusted OR (Model 2) for wave (base = first wave). Higher ACCI/CFS scores indicate higher burden of comorbidity/frailty. Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital.



data are not adjusted for important differences in patient demographics, such as age and comorbidities, our data provide more detailed insights.

Since data from other countries regarding the second wave, particularly as observed in Europe, are only slowly becoming available, an international comparison is difficult. A study from Japan, where SARS-CoV-2 infection cases rose again during June and July 2020, reported lower mortality for patients admitted during their second wave (1.2% vs 7.3%) [24]. Similarly, two different database studies from the US reported 22.8% mortality based on data from spring 2020 and 13.6% for data from April to October 2020 [25, 26]. More easily comparable data from Europe can be found in a Spanish study that reported slightly lower mortality (17% vs 15%) and a significantly lower risk for death in the second wave (aOR 0.52, 95% CI 0.31–0.85) [27]. However, their adjustment model was based on factors very different from ours, namely diabetes, age, lymphocytes, oxygen saturation and pH [27]. In contrast, figures from French ICU patients showed the same lack of change in mortality as our own data (50% vs 52%) while also noting that treatment regimens differed between waves, particularly regarding anticoagulation and glucocorticoid use [28].

The analysis of prognostic indicators in our sample showed ACCI and age as strong predictors of in-hospital mortality. However, they do not represent life expectancy and quality of life accurately. Thus, when, during a crisis such as the current pandemic, resources are limited and decisions have to be made on which patients profit the most from intensive care, more factors should be considered. This has already been recognised by the Swiss Academy of Medical Sciences (SAMS) and the Swiss Society of Intensive Care Medicine, which developed and revised the national guidelines for ICU triage. These guidelines do not include age as a direct decision criterion. Instead, frailty (as measured by the CFS) was added as an important criterion for risk prediction in November 2020 [17, 29]. This recommendation is reflected in our data, as patients with a higher frailty score were less likely to be admitted to the ICU, especially during the second wave. However, we found no significant association between the CFS and in-hospital mortality, and its predictive accuracy was noticeably lower than that of age or ACCI. If validated in larger studies, the use

Table 3: Association of baseline characteristics and vital signs upon admission stratified by all-cause in-hospital mortality.

Factor	Survivors (n = 394)	Non-Survivors (n = 92)	p-value*	AUC (95% CI)	aOR (95% CI), p-value *Model 2*
Pre-admission history					
Age (years), mean ± SD	64.0 ± 15.0	74.2 ± 9.8	**<0.01**	0.71 (0.66–0.76)	**1.07 (1.02–1.12), <0.01**
Age ≥65 years, n (%)	197 (50.0%)	79 (85.9%)	**<0.01**	0.68 (0.64–0.72)	**4.47 (1.63–12.26), <0.01**
Sex, male, n (%)	249 (63.2%)	68 (73.9%)	**0.05**	0.55 (0.50–0.60)	**2.35 (1.02–5.42), 0.04**
Transfer from other hospital, n (%)	86 (21.8%)	24 (26.1%)	0.38	0.52 (0.47–0.57)	1.06 (0.44–2.53), 0.90
Time from symptom onset to admission (days), median (IQR)	7.0 (4.0–10.0)	7.0 (3.0–9.0)	0.27	0.46 (0.38–0.54)	0.97 (0.91–1.04), 0.37
Pre-existing home medication, n (%)	319 (81.2%)	87 (94.6%)	**<0.01**	0.57 (0.54–0.60)	1.38 (0.37–5.12), 0.63
– Immunomodulating medication, n (%)	33 (8.4%)	11 (12.0%)	0.28	0.52 (0.48–0.55)	1.44 (0.51–4.04), 0.49
Presentation to emergency department					
Supplemental oxygen administered, n (%)	66 (16.8%)	45 (48.9%)	**<0.01**	0.66 (0.61–0.72)	**7.33 (3.28–16.38), <0.01**
FiO_2 (%), mean ± SD	59.0 ± 28.5	72.0 ± 26.7	**0.02**	0.64 (0.54–0.74)	**1.05 (1.01–1.08), 0.01**
Heart rate (bpm), mean ± SD	88.9 ± 16.4	93.2 ± 22.9	0.06	0.57 (0.50–0.64)	1.01 (0.99–1.03), 0.20
Respiratory rate (rpm), mean ± SD	20.7 ± 7.2	21.0 ± 11.0	0.80	0.53 (0.44–0.62)	1.04 (0.99–1.09), 0.10
Temperature (°C), mean ± SD	37.7 ± 0.9	37.6 ± 1.0	0.52	0.48 (0.41–0.56)	0.96 (0.64–1.43), 0.83
Comorbidities					
ACCI, median (IQR)	3.0 (2.0–5.0)	5.0 (4.0–7.0)	**<0.01**	0.73 (0.69–0.78)	**1.27 (1.09–1.48), <0.01**
ACCI ≥4 points, n (%)	158 (40.1%)	74 (80.4%)	**<0.01**	0.70 (0.65–0.75)	2.94 (0.94–9.24), 0.07
CFS, median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–6.0)	**<0.01**	0.67 (0.60–0.73)	1.18 (0.90–1.55), 0.23
CFS ≥4 points, n (%)	169 (42.9%)	66 (71.7%)	**<0.01**	0.64 (0.59–0.70)	1.02 (0.29–3.62), 0.98
Smoker, n (%)	33 (12.6%)	7 (10.8%)	0.69	0.49 (0.45–0.53)	0.80 (0.21–3.01), 0.74
Obesity (BMI >30 kg/m^2), n (%)	118 (30.6%)	24 (28.2%)	0.66	0.49 (0.43–0.54)	0.62 (0.28–1.39), 0.25
Diabetes, n (%)	109 (27.7%)	32 (34.8%)	0.18	0.54 (0.48–0.59)	1.05 (0.49–2.22), 0.90
Hypertension, n (%)	220 (55.8%)	62 (67.4%)	**0.04**	0.56 (0.50–0.61)	0.58 (0.27–1.25), 0.16
Coronary artery disease, n (%)	61 (15.5%)	32 (34.8%)	**<0.01**	0.60 (0.54–0.65)	1.09 (0.47–2.50), 0.85
Chronic heart failure (LVEF <40%), n (%)	11 (2.8%)	3 (3.3%)	0.80	0.50 (0.48–0.52)	0.56 (0.06–5.37), 0.61
Bronchial asthma, n (%)	24 (6.1%)	5 (5.4%)	0.81	0.50 (0.47–0.52)	1.34 (0.34–5.21), 0.67
COPD, n (%)	25 (6.3%)	10 (10.9%)	0.13	0.52 (0.49–0.56)	1.80 (0.61–5.34), 0.29
OSAS, n (%)	31 (7.9%)	15 (16.3%)	**0.01**	0.54 (0.50–0.58)	1.28 (0.46–3.57), 0.63
Solid organ transplant, n (%)	9 (2.3%)	1 (1.1%)	0.47	0.49 (0.48–0.51)	0.20 (0.02–2.31), 0.20
Active rheumatic disease, n (%)	8 (2.0%)	5 (5.4%)	0.07	0.52 (0.49–0.54)	4.33 (0.85–22.17), 0.08
Cancer, n (%)	38 (9.6%)	19 (20.7%)	**<0.01**	0.56 (0.51–0.60)	0.47 (0.15–1.43), 0.18
Liver cirrhosis, n (%)	2 (0.5%)	2 (2.2%)	0.11	0.51 (0.49–0.52)	n.a.
Chronic kidney disease, n (%)	68 (17.3%)	38 (41.3%)	**<0.01**	0.62 (0.57–0.67)	**2.25 (1.02–4.96), 0.04**

ACCI = age-adjusted Charlson comorbidity index; aOR = adjusted odds ratio; AUC = area under the receiver operating characteristic curve; BMI = body mass index; bpm = beats per minute; CFS = clinical frailty scale; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; LVEF = left ventricular ejection fraction; OSAS = obstructive sleep apnoea syndrome; rpm = respirations per minute; SD = standard deviation; n.a. = not applicable Bold values denote statistical significance at the p ≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital

of frailty instead of age for making decisions regarding the most effective allocation of resources may be challenged.

Patient management is another important area where efficacy is key. In this regard, our results show a substantial decrease in LOS during the second wave (9 vs 6.5 days), indicating improved discharge processes. There are several possible reasons for this reduction. First, more patients were discharged to rehabilitation care during the second wave, allowing shorter hospital stays as many rehabilitation clinics changed their admission criteria over the course of the pandemic. At the same time, the number of patients needing rehabilitation care after elective surgery decreased markedly during the pandemic, opening up rehabilitation beds for other patients. Second, the use of high-dose glucocorticoids may have blunted the inflammatory response in some patients, allowing earlier discharge. Similar findings have already been observed in our trial investigating community-acquired pneumonia [30]. Third, fewer patients were enrolled in therapeutic trials, which might have prevented discharge until study-drug administration was completed. Finally, the increased experience of healthcare teams regarding the management of COVID-19 patients may have translated into earlier discharge decisions.

Other recent studies report median LOS ranging from 3 days in Iran during spring 2020 [31] to 8 days in Germany (spring-summer 2020) [32] and 8.9 days in the US (spring 2020). A different study from the US using data from April to October 2020 found a median LOS of 5 days, suggesting that other regions also see a reduction in LOS similar to ours [25]. More recently, a Spanish report also found a shorter LOS during the second wave (10 vs 9 days, p <0.01) [27]. However, their LOS was noticeably longer

Table 4: Association and discrimination of baseline characteristics and vital signs upon admission stratified by ICU admission.

Factor	No ICU (n = 394)	ICU admission (n = 92	p-value*	AUC (95% CI)	aOR (95% CI), p-value *Model 2*
Pre-admission history					
Age (years), mean ± SD	66.6 ± 15.4	63.2 ± 11.0	**0.05**	0.41 (0.35–0.46)	1.00 (0.97–1.03), 0.88
Age ≥65 years, n (%)	233 (59.1%)	43 (46.7%)	**0.03**	0.44 (0.38–0.50)	0.84 (0.38–1.84), 0.66
Sex, male, n (%)	245 (62.2%)	72 (78.3%)	**<0.01**	0.58 (0.53–0.63)	**2.96 (1.33–6.59), 0.01**
Transfer from other hospital, n (%)	68 (17.3%)	42 (45.7%)	**<0.01**	0.64 (0.59–0.70)	**4.43 (2.28–8.63), <0.01**
Time from symptom onset to admission (days), median (IQR)	7.0 (4.0–9.0)	8.0 (5.0–10.0)	**0.04**	0.57 (0.51–0.64)	1.02 (0.96–1.08), 0.56
Pre-existing home medication, n (%)	327 (83.0%)	79 (86.8%)	0.37	0.52 (0.48–0.56)	**2.94 (1.19–7.29), 0.02**
– Immunomodulating medication, n (%)	37 (9.4%)	7 (7.6%)	0.59	0.49 (0.46–0.52)	0.51 (0.14–1.86), 0.31
Presentation to emergency department					
Supplemental oxygen administered, n (%)	62 (15.7%)	49 (53.3%)	**<0.01**	0.69 (0.63–0.74)	**5.71 (2.83–11.53), <0.01**
FiO_2 (%), mean ± SD	53.3 ± 25.8	78.3 ± 25.3	**<0.01**	0.75 (0.66–0.84)	**1.06 (1.02–1.09), <0.01**
Heart rate (bpm), mean ± SD	89.5 ± 17.9	91.1 ± 18.5	0.51	0.52 (0.44–0.59)	1.00 (0.98–1.02), 0.81
Respiratory rate (rpm), mean ± SD	20.9 ± 7.0	20.6 ± 11.4	0.85	0.54 (0.45–0.64)	1.02 (0.98–1.07), 0.31
Temperature (°C), mean ± SD	37.6 ± 1.0	37.8 ± 0.7	0.24	0.55 (0.49–0.62)	1.00 (0.69–1.44), 0.99
Comorbidities					
ACCI, median (IQR)	4.0 (2.0–6.0)	3.0 (2.0–4.0)	**<0.01**	0.41 (0.36–0.47)	1.03 (0.87–1.22), 0.72
ACCI ≥4 points, n (%)	201 (51.0%)	31 (33.7%)	**<0.01**	0.41 (0.36–0.47)	0.42 (0.13–1.36), 0.15
CFS, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–3.0)	**<0.01**	0.34 (0.28–0.40)	**0.66 (0.46–0.92), 0.02**
CFS ≥4 points, n (%)	198 (50.3%)	37 (40.2%)	0.08	0.45 (0.39–0.51)	1.34 (0.35–5.18), 0.67
Smoker, n (%)	32 (12.3%)	8 (11.9%)	0.93	0.50 (0.45–0.54)	1.54 (0.57–4.17), 0.39
Obesity (BMI >30 kg/m^2), n (%)	108 (28.1%)	34 (40.0%)	0.03	0.56 (0.50–0.62)	1.99 (1.03–3.85), 0.04
Diabetes, n (%)	113 (28.7%)	28 (30.4%)	0.74	0.51 (0.46–0.56)	1.47 (0.68–3.16), 0.33
Hypertension, n (%)	233 (59.1%)	49 (53.3%)	0.30	0.47 (0.41–0.53)	0.94 (0.49–1.80), 0.85
Coronary artery disease, n (%)	75 (19.0%)	18 (19.6%)	0.91	0.50 (0.46–0.55)	1.30 (0.56–3.05), 0.54
Chronic heart failure (LVEF <40%), n (%)	13 (3.3%)	1 (1.1%)	0.26	0.49 (0.48–0.50)	1.30 (0.13–13.03), 0.82
Bronchial asthma, n (%)	23 (5.8%)	6 (6.5%)	0.80	0.50 (0.48–0.53)	0.94 (0.28–3.17), 0.92
COPD, n (%)	31 (7.9%)	4 (4.3%)	0.24	0.48 (0.46–0.51)	1.06 (0.26–4.33), 0.93
OSAS, n (%)	35 (8.9%)	11 (12.0%)	0.36	0.52 (0.48–0.55)	1.68 (0.63–4.53), 0.30
Solid organ transplant, n (%)	9 (2.3%)	1 (1.1%)	0.47	0.49 (0.48–0.51)	0.79 (0.06–11.3), 0.86
Active rheumatic disease, n (%)	9 (2.3%)	4 (4.3%)	0.27	0.51 (0.49–0.53)	3.81 (0.66–22.12), 0.14
Cancer, n (%)	50 (12.7%)	7 (7.6%)	0.17	0.47 (0.44–0.51)	1.13 (0.33–3.86), 0.85
Liver cirrhosis, n (%)	4 (1.0%)	0 (0.0%)	0.33	0.49 (0.49–0.50)	n.a.
Chronic kidney disease, n (%)	93 (23.6%)	13 (14.1%)	**0.05**	0.45 (0.41–0.49)	1.50 (0.59–3.77), 0.39

ACCI = age-adjusted Charlson comorbidity index; AUC = area under the receiver operating characteristic curve; BMI = body mass index; bpm = beats per minute; CFS = clinical frailty scale; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FiO2 = fraction of inspired oxygen; IQR = interquartile range; LVEF = left ventricular ejection fraction; OR = odds ratio; OSAS = obstructive sleep apnoea syndrome; rpm = respirations per minute; SD = standard deviation; n.a. = not applicable Bold values denote statistical significance at the p ≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital

than ours and unadjusted. Further data regarding LOS in the second wave are scarce. Recently, a Swiss-wide surveillance study of patients hospitalised between February and September 2020 was published but did not include data on LOS [19]. Hence, further research on patient characteristics, predictors and outcomes is urgently needed, so we do not miss the opportunity to adjust and improve treatment and management accordingly.

Limitations

There are certain limitations to our study. First, our findings are limited to hospitalised patients in a single centre. Our analysis might have also missed factors that are responsible for both COVID-19-related mortality and prevention of hospitalisation at our clinic. Another important limitation is missing data in our data set, which mostly concerned vital signs and were not available for up to a third of patients. Further data was missing for symptom start and the CFS (24% and 13%, respectively), two important factors featured in our adjusted regression models. Thus, as observations were dropped for the multiple logistic regression models, power was reduced and representativeness of the results might be biased. However, we deemed both factors too important to exclude them from our analysis. Furthermore, we had to exclude four patients who were still hospitalised when data collection closed, thus possibly introducing a bias based on disease severity. Finally, our analysis was not adjusted for multiple comparisons, which may have increased the risk for type I errors and our results in this regard should be considered hypothesis-generating and not final.

Conclusion

This analysis provides insights into consecutively hospitalised patients with confirmed COVID-19 at a Swiss tertiary care hospital during the first and second wave of the pandemic. While treatment regimens clearly differed, mortality and ICU admission remained largely unchanged. However, the reduced LOS and increased discharge rate to rehabilitation clinics suggest patient management became more efficient over the course of the pandemic.

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Appendix

Supplementary tables

Table S1: Outcomes overall and stratified by wave. Odds ratios and regression coefficients for wave (base = first wave).

	Overall (n = 486)	First wave (n = 100)	Second wave (n = 386	p-value*	OR/coefficient† (95% CI), p-value		
					Unadjusted	*Model 1*	*Model 2*
All-cause in-hospital mortality, n (%)	92 (18.9%)	19 (19.0%)	73 (18.9%)	0.98	0.99 (0.57 to 1.74), 0.98	1.27 (0.60 to 2.67), 0.53	1.18 (0.49 to 2.80), 0.71
Time to death (days), median (IQR)	10.0 (4.0–19.0)	15.0 (5.0–24.0)	9.0 (4.0–17.0)	0.07	−3.86* (−8.50 to 0.79), 0.10	−0.55* (−6.50 to 5.40), 0.85	−0.68* (−6.14 to 4.77), 0.80
ICU admission, n (%)	92 (18.9%)	24 (24.0%)	68 (17.6%)	0.15	0.68 (0.40 to 1.15), 0.15	0.70 (0.36 to 1.35), 0.29	0.98 (0.46 to 2.06), 0.95
Time to ICU (days), median (IQR)	1.0 (0.0–3.0)	0.5 (0.0–3.0)	1.0 (0.0–4.0)	0.70	0.34* (−1.81 to 2.50), 0.75	−0.16* (−3.02 to 2.69), 0.91	−0.10* (−2.12 to 1.92), 0.92
ICU LOS (days), median (IQR)	9.0 (4.0–15.0)	9.0 (4.0–19.0)	9.0 (4.0–14.0)	0.59	−2.92* (−7.00 to 1.16), 0.16	−1.36* (−5.50 to 2.78), 0.51	−1.78* (−6.45 to 2.89), 0.45
Invasive ventilation, n (%)	65 (13.4%)	19 (19.0%)	46 (11.9%)	0.06	0.58 (0.32 to 1.04), 0.07	0.61 (0.29 to 1.31), 0.21	0.73 (0.33 to 1.64), 0.44
Hospital LOS (days), median (IQR)	7.0 (4.0–13.0)	9.0 (4.5–15.0)	6.5 (3.0–13.0)	**0.03**	−1.91* (−4.05 to 0.23), 0.08	−1.28* (−3.70 to 1.13), 0.30	**−2.53* (−4.51 to −0.54), 0.01**
Discharge status‡							
– Home care, n (%)	185 (38.1%)	47 (47.0%)	138 (35.8%)	**0.04**	**0.63 (0.40 to 0.98), 0.04**	0.60 (0.33 to 1.07), 0.08	0.55 (0.29 to 1.03), 0.06
– Rehabilitation care, n (%)	137 (28.2%)	18 (18.0%)	119 (30.8%)	**0.01**	**2.03 (1.17 to 3.53), 0.01**	1.56 (0.87 to 2.80), 0.14	**2.06 (1.04 to 4.07), 0.04**
– Other hospital, n (%)	51 (10.5%)	16 (16.0%)	35 (9.1%)	**0.04**	**0.52 (0.28 to 0.99), 0.05**	0.53 (0.24 to 1.17), 0.12	0.58 (0.24 to 1.37), 0.21
– Nursing facility	20 (4.1%)	0 (0.0%)	20 (5.2%)	**0.02**	n.a.	n.a.	n.a.
– Unknown	1 (0.2%)	0 (0.0%)	1 (0.3%)	0.61	n.a.	n.a.	n.a.

ACCI = age-adjusted Charlson comorbidity index; CFS = clinical frailty scale; CI = confidence interval; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; n.a. = not applicable; OR = odds ratio Bold values denote statistical significance at the p ≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables † Regression coefficients for continuous dependent variables ‡ Other than death Model 1 adjusted for sex, ACCI, CFS, immunomodulating home medication Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital.

Table S2: Association of baseline characteristics and vital signs upon admission stratified by all-cause in-hospital mortality.

Factor	Survivors (n = 394)	Non-Survivors (n = 92)	p-value*	AUC (95%-CI)	OR (95% CI), p-value	aOR (95% CI), p-value	
					Unadjusted	*Model 1*	*Model 2*
Pre-admission history							
Age (years), mean ± SD	64.0 ± 15.0	74.2 ± 9.8	**<0.01**	0.71 (0.66–0.76)	**1.06 (1.04–1.08), <0.01**	1.03 (1.00–1.06), 0.09	**1.07 (1.02–1.12), <0.01**
Age ≥65 years, n (%)	197 (50.0%)	79 (85.9%)	**<0.01**	0.68 (0.64–0.72)	**6.08 (3.27–11.29), <0.01**	**2.99 (1.31–6.85), <0.01**	**4.47 (1.63–12.26), <0.01**
Sex, male, n (%)	249 (63.2%)	68 (73.9%)	**0.05**	0.55 (0.50–0.60)	**1.65 (0.99–2.74), 0.05**	**1.92 (1.02–3.63), 0.04**	**2.35 (1.02–5.42), 0.04**
Transfer from other hospital, n (%)	86 (21.8%)	24 (26.1%)	0.38	0.52 (0.47–0.57)	1.26 (0.75–2.13), 0.38	1.09 (0.55–2.16), 0.80	1.06 (0.44–2.53), 0.90
Time from symptom onset to admission (days), median (IQR)	7.0 (4.0–10.0)	7.0 (3.0–9.0)	0.27	0.46 (0.38–0.54)	0.99 (0.94–1.05), 0.74	0.97 (0.91–1.04), 0.38	0.97 (0.91–1.04), 0.37
Pre-existing home medication, n (%)	319 (81.2%)	87 (94.6%)	**<0.01**	0.57 (0.54–0.60)	**4.04 (1.58–10.29), <0.01**	1.10 (0.39–3.16), 0.85	1.38 (0.37–5.12), 0.63
– Immunomodulating medication, n (%)	33 (8.4%)	11 (12.0%)	0.28	0.52 (0.48–0.55)	1.49 (0.72–3.06), 0.28	1.05 (0.43–2.54), 0.92	1.44 (0.51–4.04), 0.49
Presentation to emergency department							
Supplemental oxygen administered, n (%)	66 (16.8%)	45 (48.9%)	**<0.01**	0.66 (0.61–0.72)	**4.76 (2.92–7.74), <0.01**	**4.08 (2.22–7.49), <0.01**	**7.33 (3.28–16.38), <0.01**
FiO_2 (%), mean ± SD	59.0 ± 28.5	72.0 ± 26.7	**0.02**	0.64 (0.54–0.74)	**1.02 (1.00–1.03), 0.02**	**1.02 (1.00–1.04), 0.05**	**1.05 (1.01–1.08), 0.01**
Heart rate (bpm), mean ± SD	88.9 ± 16.4	93.2 ± 22.9	0.06	0.57 (0.50–0.64)	1.01 (1.00–1.03), 0.06	1.01 (0.99–1.02), 0.42	1.01 (0.99–1.03), 0.20
Respiratory rate (rpm), mean ± SD	20.7 ± 7.2	21.0 ± 11.0	0.80	0.53 (0.44–0.62)	1.00 (0.97–1.04), 0.80	1.02 (0.98–1.07), 0.27	1.04 (0.99–1.09), 0.10
Temperature (°C), mean ± SD	37.7 ± 0.9	37.6 ± 1.0	0.52	0.48 (0.41–0.56)	0.92 (0.71–1.19), 0.52	0.90 (0.65–1.23), 0.51	0.96 (0.64–1.43), 0.83
Comorbidities							
ACCI, median (IQR)	3.0 (2.0–5.0)	5.0 (4.0–7.0)	**<0.01**	0.73 (0.69–0.78)	**1.33 (1.22–1.46), <0.01**	**1.25 (1.11–1.41), <0.01**	**1.27 (1.09–1.48), <0.01**
ACCI ≥4 points, n (%)	158 (40.1%)	74 (80.4%)	**<0.01**	0.70 (0.65–0.75)	**6.14 (3.53–10.68), <0.01**	**3.35 (1.29–8.67), 0.01**	2.94 (0.94–9.24), 0.07
CFS, median (IQR)	3.0 (2.0–4.0)	4.0 (3.0–6.0)	**<0.01**	0.67 (0.60–0.73)	**1.39 (1.20–1.61), <0.01**	**1.20 (1.00–1.45), 0.05**	1.18 (0.90–1.55), 0.23
CFS ≥4 points, n (%)	169 (42.9%)	66 (71.7%)	**<0.01**	0.64 (0.59–0.70)	**3.38 (2.06–5.55), <0.01**	0.88 (0.33–2.33), 0.80	1.02 (0.29–3.62), 0.98
Smoker, n (%)	33 (12.6%)	7 (10.8%)	0.69	0.49 (0.45–0.53)	0.84 (0.35–1.99), 0.69	0.88 (0.32–2.44), 0.81	0.80 (0.21–3.01), 0.74
Obesity (BMI >30 kg/m^2), n (%)	118 (30.6%)	24 (28.2%)	0.66	0.49 (0.43–0.54)	0.89 (0.53–1.50), 0.66	0.87 (0.46–1.64), 0.66	0.62 (0.28–1.39), 0.25
Diabetes, n (%)	109 (27.7%)	32 (34.8%)	0.18	0.54 (0.48–0.59)	1.39 (0.86–2.26), 0.18	0.83 (0.45–1.53), 0.55	1.05 (0.49–2.22), 0.90
Hypertension, n (%)	220 (55.8%)	62 (67.4%)	**0.04**	0.56 (0.50–0.61)	**1.63 (1.01–2.64), 0.04**	0.60 (0.33–1.11), 0.11	0.58 (0.27–1.25), 0.16
Coronary artery disease, n (%)	61 (15.5%)	32 (34.8%)	**<0.01**	0.60 (0.54–0.65)	**2.91 (1.75–4.84), <0.01**	1.31 (0.67–2.58), 0.43	1.09 (0.47–2.50), 0.85
Chronic heart failure (LVEF<40%), n (%)	11 (2.8%)	3 (3.3%)	0.80	0.50 (0.48–0.52)	1.19 (0.32–4.34), 0.80	0.72 (0.19–2.80), 0.64	0.56 (0.06–5.37), 0.61

Factor	Survivors (n = 394)	Non-Survivors (n = 92)	p-value*	AUC (95%-CI)	OR (95% CI), p-value	aOR (95% CI), p-value	
					Unadjusted	*Model 1*	*Model 2*
Bronchial asthma, n (%)	24 (6.1%)	5 (5.4%)	0.81	0.50 (0.47–0.52)	0.89 (0.33–2.39), 0.81	1.55 (0.48–5.01), 0.47	1.34 (0.34–5.21), 0.67
COPD, n (%)	25 (6.3%)	10 (10.9%)	0.13	0.52 (0.49–0.56)	1.80 (0.83–3.89), 0.14	1.30 (0.56–3.00), 0.54	1.80 (0.61–5.34), 0.29
OSAS, n (%)	31 (7.9%)	15 (16.3%)	**0.01**	0.54 (0.50–0.58)	**2.28 (1.17–4.43), 0.01**	1.34 (0.57–3.11), 0.50	1.28 (0.46–3.57), 0.63
Solid organ transplant, n (%)	9 (2.3%)	1 (1.1%)	0.47	0.49 (0.48–0.51)	0.47 (0.06–3.76), 0.48	0.23 (0.02–2.33), 0.22	0.20 (0.02–2.31), 0.20
Active rheumatic disease, n (%)	8 (2.0%)	5 (5.4%)	0.07	0.52 (0.49–0.54)	2.77 (0.89–8.68), 0.08	**4.5 (0.97–20.94), 0.05**	4.33 (0.85–22.17), 0.08
Cancer, n (%)	38 (9.6%)	19 (20.7%)	**<0.01**	0.56 (0.51–0.60)	**2.44 (1.33–4.47), <0.01**	1.00 (0.46–2.20), 1.00	0.47 (0.15–1.43), 0.18
Liver cirrhosis, n (%)	2 (0.5%)	2 (2.2%)	0.11	0.51 (0.49–0.52)	4.36 (0.61–31.34), 0.14	2.45 (0.33–18.27), 0.38	n.a.
Chronic kidney disease, n (%)	68 (17.3%)	38 (41.3%)	**<0.01**	0.62 (0.57–0.67)	**3.37 (2.07–5.51), <0.01**	**2.16 (1.16–4.01), 0.01**	**2.25 (1.02–4.96), 0.04**

ACCI = age-adjusted Charlson comorbidity index; aOR = adjusted odds ratio; AUC = area under the receiver operating characteristic curve; BMI = body mass index; bpm = beats per minute; CFS = clinical frailty scale; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; LVEF = left ventricular ejection fraction; OR = odds ratio; OSAS = obstructive sleep apnoea syndrome; rpm = respirations per minute; SD = standard deviation; n.a. = not applicable Bold values denote statistical significance at the p ≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables Model 1 adjusted for sex, ACCI, CFS, immunomodulating home medication Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital

Table S3: Association and discrimination of baseline characteristics and vital signs upon admission stratified by ICU admission.

Factor	No ICU (n = 394)	ICU admission (n = 92)	p-value*	AUC (95% CI)	OR (95% CI), p-value	aOR (95% CI), p-value	
					Unadjusted	*Model 1*	*Model 2*
Pre-admission history							
Age (years), mean ± SD	66.6 ± 15.4	63.2 ± 11.0	**0.05**	0.41 (0.35–0.46)	**0.98 (0.97–1.00), 0.05**	1.01 (0.98–1.04), 0.49	1.00 (0.97–1.03), 0.88
Age ≥65 years, n (%)	233 (59.1%)	43 (46.7%)	**0.03**	0.44 (0.38–0.50)	**0.61 (0.38–0.96), 0.03**	1.07 (0.52–2.19), 0.86	0.84 (0.38–1.84), 0.66
Sex, male, n (%)	245 (62.2%)	72 (78.3%)	**<0.01**	0.58 (0.53–0.63)	**2.19 (1.28–3.74), <0.01**	**2.34 (1.18–4.63), 0.02**	**2.96 (1.33–6.59), 0.01**
Transfer from other hospital, n (%)	68 (17.3%)	42 (45.7%)	**<0.01**	0.64 (0.59–0.70)	**4.03 (2.48–6.55), <0.01**	**4.04 (2.22–7.36), <0.01**	**4.43 (2.28–8.63), <0.01**
Time from symptom onset to admission (days), median (IQR)	7.0 (4.0–9.0)	8.0 (5.0–10.0)	**0.04**	0.57 (0.51–0.64)	**1.06 (1.01–1.10), 0.02**	1.02 (0.97–1.08), 0.40	1.02 (0.96–1.08), 0.56
Pre-existing home medication, n (%)	327 (83.0%)	79 (86.8%)	0.37	0.52 (0.48–0.56)	1.35 (0.70–2.61), 0.38	**2.66 (1.18–6.00), 0.02**	**2.94 (1.19–7.29), 0.02**
– Immunomodulating medication, n (%)	37 (9.4%)	7 (7.6%)	0.59	0.49 (0.46–0.52)	0.79 (0.34–1.84), 0.59	0.67 (0.22–2.01), 0.47	0.51 (0.14–1.86), 0.31
Presentation to emergency department							
Supplemental oxygen administered, n (%)	62 (15.7%)	49 (53.3%)	**<0.01**	0.69 (0.63–0.74)	**6.10 (3.73–9.97), <0.01**	**6.10 (3.35–11.09), <0.01**	**5.71 (2.83–11.53), <0.01**
FiO_2 (%), mean ± SD	53.3 ± 25.8	78.3 ± 25.3	**<0.01**	0.75 (0.66–0.84)	**1.04 (1.02–1.05), <0.01**	**1.05 (1.02–1.08), <0.01**	**1.06 (1.02–1.09), <0.01**
Heart rate (bpm), mean ± SD	89.5 ± 17.9	91.1 ± 18.5	0.51	0.52 (0.44–0.59)	1.00 (0.99–1.02), 0.51	0.99 (0.98–1.01), 0.61	1.00 (0.98–1.02), 0.81
Respiratory rate (rpm), mean ± SD	20.9 ± 7.0	20.6 ± 11.4	0.85	0.54 (0.45–0.64)	1.00 (0.96–1.03), 0.85	1.02 (0.98–1.07), 0.28	1.02 (0.98–1.07), 0.31
Temperature (°C), mean ± SD	37.6 ± 1.0	37.8 ± 0.7	0.24	0.55 (0.49–0.62)	1.17 (0.90–1.53), 0.24	1.01 (0.73–1.39), 0.97	1.00 (0.69–1.44), 0.99
Comorbidities							
ACCI, median (IQR)	4.0 (2.0–6.0)	3.0 (2.0–4.0)	**<0.01**	0.41 (0.36–0.47)	**0.86 (0.78–0.95), <0.01**	0.96 (0.84–1.11), 0.61	1.03 (0.87–1.22), 0.72
ACCI ≥4 points, n (%)	201 (51.0%)	31 (33.7%)	**<0.01**	0.41 (0.36–0.47)	**0.49 (0.30–0.79), <0.01**	0.47 (0.17–1.32), 0.15	0.42 (0.13–1.36), 0.15
CFS, median (IQR)	3.0 (2.0–5.0)	3.0 (2.0–3.0)	**<0.01**	0.34 (0.28–0.40)	**0.61 (0.48–0.76), <0.01**	**0.67 (0.51–0.88), <0.01**	**0.66 (0.46–0.92), 0.02**
CFS ≥4 points, n (%)	198 (50.3%)	37 (40.2%)	0.08	0.45 (0.39–0.51)	0.67 (0.42–1.06), 0.08	1.23 (0.38–4.02), 0.73	1.34 (0.35–5.18), 0.67
Smoker, n (%)	32 (12.3%)	8 (11.9%)	0.93	0.50 (0.45–0.54)	0.97 (0.42–2.21), 0.93	1.03 (0.41–2.57), 0.95	1.54 (0.57–4.17), 0.39
Obesity (BMI >30 kg/m^2), n (%)	108 (28.1%)	34 (40.0%)	0.03	0.56 (0.50–0.62)	1.71 (1.05–2.78), 0.03	1.61 (0.90–2.89), 0.11	1.99 (1.03–3.85), 0.04
Diabetes, n (%)	113 (28.7%)	28 (30.4%)	0.74	0.51 (0.46–0.56)	1.09 (0.66–1.78), 0.74	1.25 (0.63–2.47), 0.52	1.47 (0.68–3.16), 0.33
Hypertension, n (%)	233 (59.1%)	49 (53.3%)	0.30	0.47 (0.41–0.53)	0.79 (0.50–1.24), 0.30	0.91 (0.51–1.64), 0.75	0.94 (0.49–1.80), 0.85
Coronary artery disease, n (%)	75 (19.0%)	18 (19.6%)	0.91	0.50 (0.46–0.55)	1.03 (0.58–1.84), 0.91	1.14 (0.52–2.51), 0.74	1.30 (0.56–3.05), 0.54
Chronic heart failure (LVEF<40%), n (%)	13 (3.3%)	1 (1.1%)	0.26	0.49 (0.48–0.50)	0.33 (0.04–2.52), 0.28	0.79 (0.09–6.60), 0.83	1.30 (0.13–13.03), 0.82

Factor	No ICU (n = 394)	ICU admission (n = 92)	p-value*	AUC (95% CI)	OR (95% CI), p-value	aOR (95% CI), p-value	
					Unadjusted	*Model 1*	*Model 2*
Bronchial asthma, n (%)	23 (5.8%)	6 (6.5%)	0.80	0.50 (0.48–0.53)	1.13 (0.44–2.85), 0.80	0.95 (0.30–3.02), 0.94	0.94 (0.28–3.17), 0.92
COPD, n (%)	31 (7.9%)	4 (4.3%)	0.24	0.48 (0.46–0.51)	0.53 (0.18–1.55), 0.25	1.16 (0.36–3.75), 0.80	1.06 (0.26–4.33), 0.93
OSAS, n (%)	35 (8.9%)	11 (12.0%)	0.36	0.52 (0.48–0.55)	1.39 (0.68–2.86), 0.37	1.36 (0.54–3.44), 0.51	1.68 (0.63–4.53), 0.30
Solid organ transplant, n (%)	9 (2.3%)	1 (1.1%)	0.47	0.49 (0.48–0.51)	0.47 (0.06–3.76), 0.48	0.96 (0.08–11.07), 0.98	0.79 (0.06–11.3), 0.86
Active rheumatic disease, n (%)	9 (2.3%)	4 (4.3%)	0.27	0.51 (0.49–0.53)	1.94 (0.59–6.46), 0.28	4.52 (0.86–23.72), 0.07	3.81 (0.66–22.12), 0.14
Cancer, n (%)	50 (12.7%)	7 (7.6%)	0.17	0.47 (0.44–0.51)	0.57 (0.25–1.29), 0.18	1.53 (0.56–4.16), 0.40	1.13 (0.33–3.86), 0.85
Liver cirrhosis, n (%)	4 (1.0%)	0 (0.0%)	0.33	0.49 (0.49–0.50)	n.a.	n.a.	n.a.
Chronic kidney disease, n (%)	93 (23.6%)	13 (14.1%)	**0.05**	0.45 (0.41–0.49)	**0.53 (0.28–1.00), 0.05**	1.16 (0.52–2.58), 0.72	1.50 (0.59–3.77), 0.39

ACCI = age-adjusted Charlson comorbidity index; aOR = adjusted odds ratio; AUC = area under the receiver operating characteristic curve; BMI = body mass index; bpm = beats per minute; CFS = clinical frailty scale; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; IQR = interquartile range; LVEF = left ventricular ejection fraction; OR = odds ratio; OSAS = obstructive sleep apnoea syndrome; rpm = respirations per minute; SD = standard deviation; n.a. = not applicable Bold values denote statistical significance at the p ≤0.05 level. * Wilcoxon rank-sum test for continuous variables, Pearson's chi-square test for binary variables Model 1: adjusted for sex, ACCI, CFS, immunomodulating home medication Model 2 adjusted for sex, ACCI, CFS, immunomodulating home medication, time from symptom onset to admission, transfer from other hospital