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Temporal trends of COVID-19 related in-hospital mortality and demographics in Switzerland – a retrospective single centre cohort study

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Summary

AIMS: The aim of this study was to analyse the demographics, risk factors and in-hospital mortality rates of patients admitted with coronavirus disease 2019 (COVID-19) to a tertiary care hospital in Switzerland.

METHODS: In this single-centre retrospective cohort study at the University Hospital Basel, we included all patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection hospitalised from 27 February 2020 to 10 May 2021. Patients' characteristics were extracted from the electronic medical record system. The primary outcome of this study was temporal trends of COVID-19-related in-hospital mortality. Secondary outcomes were COVID-19-related mortality in patients hospitalised on the intensive care unit (ICU), admission to ICU, renal replacement therapy and length of hospital stay, as well as a descriptive analysis of risk factors for in-hospital mortality.

RESULTS: During the study period we included 943 hospitalisations of 930 patients. The median age was 65 years (interquartile range [IQR] 53–76) and 63% were men. The numbers of elderly patients, patients with multiple comorbidities and need for renal replacement therapy decreased from the first and second to the third wave. The median length of stay and need for ICU admission were similar in all waves. Throughout the study period 88 patients (9.3%) died during the hospital stay. Crude in-hospital mortality was similar over the course of the first two waves (9.5% and 10.2%, respectively), whereas it decreased in the third wave (5.4%). Overall mortality in patients without comorbidities was low at 1.6%, but it increased in patients with any comorbidity to 12.6%. Predictors of all-cause mortality over the whole period were age (adjusted odds ratio [aOR] per 10-year increase 1.81, 95% confidence interval [CI] 1.45–2.26; p <0.001), male sex (aOR 1.68, 95% CI 1.00–2.82; p = 0.048), immunocompromising condition (aOR 2.09, 95% CI 1.01–4.33; p = 0.048) and chronic kidney disease (aOR 2.25, 95% CI 1.35–3.76; p = 0.002).

CONCLUSION: In our study in-hospital mortality was 9.5%, 10.2% and 5.4% in the first, second and third waves, respectively. Age, immunocompromising condition, male sex and chronic kidney disease were factors associated with in-hospital mortality. Importantly, patients without any comorbidity had a very low in-hospital mortality regardless of age.

Background

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, 704,620 cases of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and 10,369 deaths related to COVID-19 have been reported in Switzerland (as of 8 July 2021) [1]. Worldwide, case fatality rates ranged between 12 and 80% during the first wave. Temporal trajectories of case fatality rates greatly varied between countries, which appears to be associated with comorbidity and socioeconomic factors [2]. After the early course of the pandemic, declining in-hospital mortality rates have been reported in several countries [3–5]. Improvement of survival may be linked to improved patient management and/or change of patient demographics. However, in December 2020, the emergence of at least three variants carrying mutations have led to an additional concern. The B.1.1.7, first detected in the United Kingdom in September 2020, was reported to be considerably more contagious than the original virus. Evidence indicated that infection with this B.1.1.7 variant is associated with an increased risk of severe illness and death [6, 7].

In Switzerland, a recent national report of deaths related to COVID-19 described an overall mortality rate of 11% in hospitalised patients and 28% of patients admitted to the intensive care unit (ICU) from February 2020 to Feb-

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ruary 2021 [8]. Over time, preventive measures such as increasing vaccination of people at high risk for severe COVID-19, improved in-hospital management, preferential treatment of old and very sick patients at home or in nursing homes, and development of natural herd immunity likely have impacted patient demographics and therefore outcomes over time. Large cohorts identified older age, pulmonary or cardiovascular disease, chronic kidney disease, obesity or immunocompromising conditions as risk factors for severe disease and increased mortality; however, none of those studies included patients from Switzerland [3, 9, 10]. Also, temporal trends of COVID-19-related in-hospital mortality and changing demographic factors have not been investigated in Switzerland. To address this gap in knowledge, we conducted a retrospective study of patients hospitalised at the University Hospital Basel.

Materials and methods

Setting and study design

We conducted a single-centre retrospective cohort study at the University Hospital Basel, a tertiary care centre in Switzerland with 773 beds and 37,000 annual hospital admissions. All patients with SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction (RT-PCR) test hospitalised at the University Hospital Basel from 27 February 2020 to 10 May 2021 were included in the study. Only patients with a hospitalisation for COVID-19 or a hospitalisation complicated by a SARS-CoV-2 infection were included. Recurrent admissions of the same patient were considered as additional hospitalisations if the patient persistently tested positive for SARS-CoV-2. Patients were excluded if general informed consent was declined. Reflecting the dynamics of the epidemic in our region, we stratified the data in three periods: First, second and third waves from 27 February to 30 June 2020, 01 July 2020 to 28 February 2021 and 01 March to 10 May 2021, respectively. The electronic patient information system was screened daily by the study team for new patients admitted with positive SARS-CoV-2 RT-PCR. The data were collected and entered in a study database by trained physicians of the study team. There was no further data validation process. The study has been approved by the Ethikkommission Nordwest- und Zentralschweiz, Switzerland (Project-ID 2020-00769) and registered at ClinicalTrials.gov (NCT04351503). The study adheres to the Declaration of Helsinki.

Treatment procedures

All patients were treated according to internal treatment guidelines of the University Hospital Basel, which changed over time but were in agreement with Swiss guidance for COVID-19 from different societies such as the Society for Infectious Diseases or Intensive Medicine. During the first wave, standard care included lopinavir/ritonavir and hydroxychloroquine for all hospitalised patients. For patients with severe COVID-19, treatment included remdesivir and tocilizumab during the first wave, remdesivir and dexamethasone during the second wave, and remdesivir, dexamethasone and tocilizumab during the third wave. We used contraindications for remdesivir and tocilizumab application according to the guidance published by the Swiss Society for Infectious Diseases and the European Medicines Agency (EMA, 2020): elevated transaminase (alanine transaminase [ALT] ≥5 times the upper limit of normal) or renal impairment (estimated glomerular filtration rate [eGFR] <30 ml/minute) for remdesivir and presence of elevated liver enzymes (ALT ≥5 times the upper limit of normal) or ongoing bacterial infections for tocilizumab.

From the beginning we aimed to standardise intensive care treatment in our institution. It consisted of the usual elements for intensive care patients, depending on the number of failing organ systems. However, one main focus was the respiratory system and the treatment of acute respiratory distress syndrome. All established treatment modalities were used, from high-flow oxygen, noninvasive and invasive ventilation to extracorporeal membrane oxygenation. Prone positioning was and still is an additional key element. Another focus was on prevention and, when necessary, treatment of bacterial superinfection up to septic shock. Renal replacement therapy was started at the discretion of the treating physician whenever indicated to control fluid balance. The intensive care nurses focused on the continuous monitoring of ventilation therapy and the safe implementation of the prone position, as well as the prevention of secondary damage such as pressure ulcers.

Study outcomes and definitions

The primary outcome of this study were the temporal trends of COVID-19-related in-hospital mortality and demographics in Switzerland. Secondary outcomes were COVID-19-related mortality in patients hospitalised on the ICU, rates of admission to ICU, renal replacement therapy and length of hospital stay, as well as a descriptive analysis of risk factors for in-hospital mortality. The following patient characteristics were extracted from the electronic medical record system: age, sex and comorbidities (chronic obstructive pulmonary disease [COPD], diabetes mellitus, arterial hypertension, cardiovascular disease, immunosuppression, history of cancer and chronic kidney disease). Comorbidities were collected from the electronic medical records. COPD, diabetes, arterial hypertension, cardiovascular disease and cancer were defined as present if documented in the final discharge letter and corresponding medication was prescribed. Immunosuppression was defined as use of high-dose corticosteroids (prednisone equivalent of ≥1 mg/kg body weight in the previous 7 days) or agents to prevent graft rejection in solid organ or human stem cell or bone marrow transplantation and to treat autoimmune diseases during the last 3 months.

Chronic kidney disease was adjudicated by board-certified nephrologists and defined as a persistent eGFR below 60 ml/min/1.73 m^2 during the whole hospitalisation that was not presumed to be a cause of unrecovered acute kidney injury, using electronic medical records for the last 6 months prior to the index hospitalisation to define a baseline creatinine value. Comorbidities were recorded as assessed by the treating physician. The data-file was closed on 18 May 2021 and up to this point all patients except two (0.2%) had been discharged or had died. We adhere to the STROBE guidelines [11] in reporting our results, the checklist is provided in the appendix.

Statistical analyses

Analyses were performed using R (R Core Team 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). A two-tailed alpha level of <0.05 was considered statistically significant. Discrete variables were expressed as counts (percentage) and continuous variables as median and interquartile range [IQR]. We used the Kruskal-Wallis test and Pearson's chi-square test or Fisher's exact test for group comparison, as appropriate.

To further investigate the relationship of comorbidities, demographics and in-hospital death in an explorative way, a logistic regression model was built. A table with the number of missing values for each variable is provided in the appendix. The assumptions of logistic regression were tested as followed: linearity of continuous variables with their logit-transformed outcome was checked visually by plotting age with mortality, multicollinearity was checked using the variance inflation factor. We included all comorbidities and the demographic variable age and sex in the model. Area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the model performance and is reported in the appendix. Given the low event rate, logistic regression was not done separately for each wave. After the final model was chosen, to compare the relative importance of predictors in the model, a dominance analysis was performed using the package "dominance analysis" with the method of Azen and Traxel [12]. Briefly, the contribution of each variable to the model is assessed as the change of McFadden R when the predictor is added to the model. If the additional contribution of a variable is greater than that of another variable it is said to dominate the latter. Body mass index (BMI) was missing in 454 (48%) cases and was therefore not included in the analysis. No imputation was used to address missing values.

Results

Patients and demographics

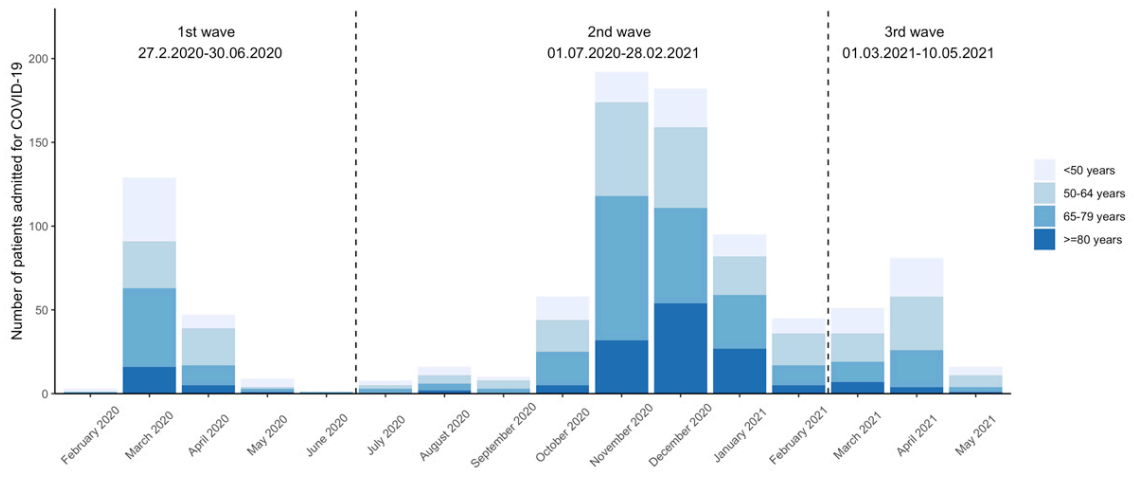
Between 27 February 2020 and 10 May 2021, 1001 patients with COVID-19 were admitted during 1022 hospitalisations at the University Hospital of Basel. After exclusion of patients with a documented refusal to give general informed consent or with recurrent hospitalisation for other reasons than COVID-19, 930 patients with 943 hospitalisations remained as study population (a flowchart is presented supplementary fig. S1 in the appendix). The baseline characteristics of the study population stratified for each wave are summarised in table 1. The median patient age was 65 years (IQR 53–76) and 596 (63%) were men. The number of admitted patients increased with age, with a majority of patients being 65–79 years of age (317 patients, 34%). Only 159 patients (17%) were older than 80 years (table 1 and fig. 1) and 686 patients (73%) had at least one comorbidity. The most common comorbidities were arterial hypertension (447 patients, 47%), cardiovascular disease (323 patients, 34%) and diabetes (265 patients, 28%). The median length of hospital stay was 7 days (IQR 5–13); 22% of all patients required intensive care treatment.

Over time, the number of older patients admitted to the hospital decreased significantly from the first and second to the third wave. Similarly, the burden of patients with multiple comorbidities decreased from the first and second to the third wave (fig. 2) The predominance of male patients remained stable during all three waves (table 1). Although the need for ICU admission was similar in all waves, the number of older patients with ICU dependency decreased in the third wave. Also, fewer patients needed renal replacement therapy over the course of the three waves (table 1 and fig. 2). Median length of stay was similar in the first and third wave (both 7 days, IQR 4–11) and peaked in the second wave (8 days, IQR 5–14; p = 0.014).

Mortality

Over the course of the three waves, 88 patients (9.3%) died during the hospitalisation. Compared with patients who survived, patients who died more often had a history of diabetes (n = 35, 40% vs n = 230, 27%), arterial hypertension

Figure 1: Hospital admission at the University Hospital of Basel between February 2020 and May 2021 stratified by age. The dashed lines indicate the first, second and third waves.



(n = 59, 67% vs n = 388, 45%), cardiovascular disease (n = 47, 53% vs n = 276, 32%), chronic kidney disease (n = 38, 43% vs n = 127, 15%) and more often required renal replacement therapy (n = 8, 9% vs n = 8, 1%) (table 2).

Crude in-hospital mortality was higher with increasing age (<50 years 1.6%, 50–64 years 2.8%, 65–79 years 13.6%, ≥80 years 21.4%). In-hospital mortality in patients requiring intensive care treatment was 28%. Over the course of the first two waves, the in-hospital mortality remained similar (first wave 9.5%, second wave 10.2%); it decreased in the third wave (5.4%). This decrease in mortality over the three waves was predominantly seen in patients older than 80 years (31.8%, 20%, and 16.7%, respectively) and in patients aged 50–64 years (3.92%, 3.39% and 0%, respectively), whereas in the age group of 65–79 years mortality remained stable (first wave 14.3%, second wave 12.9%, third wave 16.2%). Mortality in the ICU was highest in the second wave (30.7%) and was similar in the first (23.1%) and third wave (23.3%). Logistic regression revealed age (adjusted odds ratio [aOR] per 10-years increase 1.81, 95% confidence interval [CI] 1.45–2.26; p <0.001), male sex (aOR 1.68, 95% CI 1.00–2.82; p = 0.048), immunocompromising condition (aOR 2.09, 95% CI 1.01–4.33; p = 0.048) and chronic kidney disease (aOR 2.25, 95% CI 1.35–3.76; p = 0.002) to be significant predictors of all-cause mortality over the whole period (supplementary table S3, fig. 3).

Dominance analysis revealed that age and chronic kidney disease are the most important predictors in our model. However, when stratified by patients with and without comorbidities, the in-hospital mortality in patients without comorbidities was low in all age groups (1.6%), whereas it gradually increased in patients with any comorbidity (12.2%, fig. 4).

Discussion

In this retrospective analysis we investigated the temporal trends of in-hospital mortality and demographics of patients with COVID-19 hospitalised at the University Hospital Basel – the only tertiary care institution in the northwestern part of Switzerland. We report five major findings. First, we observed a decrease of older and comorbid patients in the third wave as compared with the first two waves. Second, we report a low in-hospital-mortality of 9.5%, 10.2% and 5.4% in the first, second and third waves, respectively. Third, we found a significant decrease of kidney failure dependent on renal replacement over the course of the pandemic. Fourth, we confirmed age, chronic kidney disease, male sex and immunocompromising condition as risk factors for in-hospital mortality in patients with COVID-19. Age as well as chronic kidney disease were the most dominant predictors of in-hospital death. Fifth, in-hospital mortality was lower than 2% in patients without comorbidities in all age groups.

To the best of our knowledge this is the first and most comprehensive study of hospitalised COVID-19 patients in Switzerland over the course of the pandemic. Also, in an international context such comprehensive studies over the entire time span are scarce. The decrease of older patients hospitalised for COVID-19 in the third wave compared to the first two waves is in line with the nationwide trends in Switzerland, which show a steady reduction in patients over 80 years of age since mid-December [13]. We believe that one reason for this reduction is the vaccination campaign starting at the end of December 2020 / beginning of January 2021 for people over 80, which led to an overall vaccination rate of 25% by March 2021 [1]. Additionally, a change in referral practice by nursing homes and general practitioners (e.g., because of advance directives), as well as a reduction of the population at risk due to the high mor-

Table 1: Baseline characteristics of all patients and stratified by wave.

	Overall	1st Wave	2nd Wave	3rd Wave	p-value
n = 943	n = 189 (20%)	n = 606 (64%)	n = 148 (16%)		
Age (years), median (IQR)	65 (53–76)	62 (48–73)	68 (58–78)	58 (47–69)	<0.001
Age group, n (%)					<0.001
– <50 years	183 (19)	53 (28)	87 (14)	43 (29)	
– 50–64 years	284 (30)	51 (27)	177 (29)	56 (38)	
– 65–79 years	317 (34)	63 (33)	217 (36)	37 (25)	
– ≥80 years	159 (17)	22 (12)	125 (21)	12 (8)	
Male sex, n (%)	596 (63)	115 (61)	393 (65)	88 (59)	0.352
Hospitalisation (days), median (IQR)	7 (5–13)	7 (4–11)	8 (5–14)	7 (4–11)	0.014
ICU admission, n (%)	206 (22)	39 (21)	137 (23)	30 (20)	0.774
Days in ICU, median (IQR)	8 (3–18)	10 (4–19)	8 (3–16)	9 (3–23)	0.691
COPD, n (%)	64 (7)	6 (3)	52 (9)	6 (4)	0.012
Diabetes, n (%)	265 (28)	35 (19)	199 (33)	31 (21)	<0.001
Arterial hypertension, n (%)	447 (47)	87 (46)	299 (49)	61 (41)	0.190
Cardiovascular disease, n (%)	323 (34)	47 (25)	251 (41)	25 (17)	<0.001
Immunocompromising condition, n (%)	103 (11)	25 (13)	61 (10)	17 (11)	0.437
Cancer, n (%)	160 (17)	33 (17)	114 (19)	13 (9)	0.010
Chronic kidney disease, n (%)	165 (17)	30 (16)	116 (19)	19 (13)	0.163
Renal replacement therapy during hospitalisation, n (%)	16 (2)	11 (6)	4 (1)	1 (1)	<0.001
Days on RRT, median (IQR)	8 (2–15)	8 (2–16)	4 (2–10)	14 (14, 14)	0.581

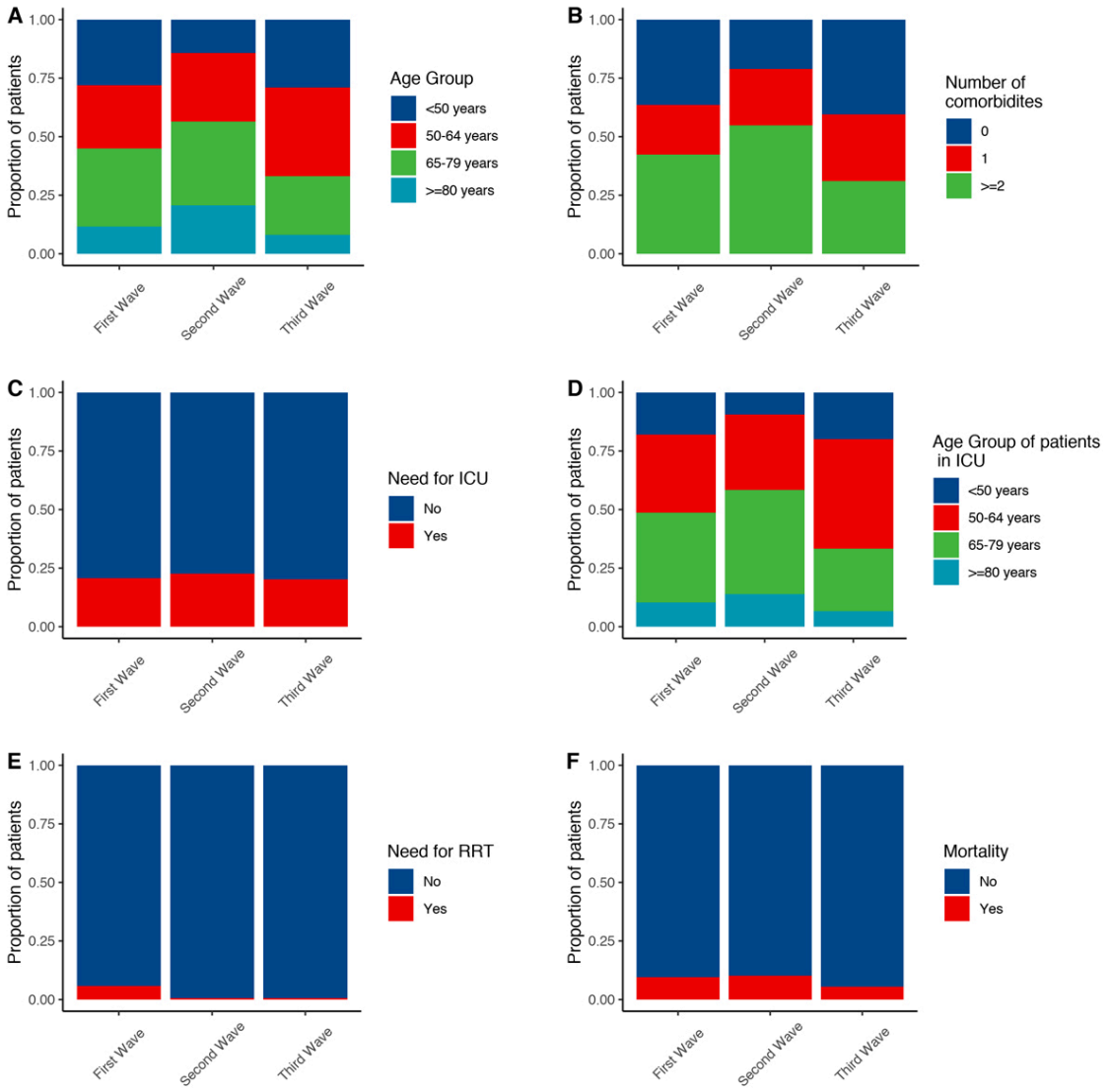
ICU = intensive care unit; COPD = chronic obstructive pulmonary disease; RRT = renal replacement therapy and was defined as renal replacement therapy during hospitalisation. The first wave was defined from 27 February to 30 June 2020, the second from 01 July 2020 to 28 February 2021 and the third from 01 March to 10 May 2021. Values are number (percentage) or median (interquartile range [IQR]). The p-values are calculated between all three waves using a Kruskal-Wallis test for continuous variables and chi-square test for categorical variables.

tality among older people in the first two waves might have also contributed to this reduction.

The in-hospital mortality of 9.5% during the first wave is lower than the in-hospital mortality rate of the first wave from other countries and centres: for example, 22% in Germany [14], 30% in the UK [15] and 18.7% in Denmark [16]. A study from Geneva (Switzerland) reported an in-hospital mortality of 15.6% [17]. There are a number of possible explanations for these different in-hospital mortality rates. First, compared with our cohort, the median age of the study population in comparable studies was higher. Second, differences in referral practice by nursing homes and general practitioners – such as not referring patients with a very high mortality risk – might also have contributed to the different in-hospital mortality. In fact, elderly patients who refused intensive care treatment in advance, were hospitalised in neighbouring geriatric hospitals. Third, during the first wave patient management and treatment procedures might not have been similar. Fourth, the proportion of patients with multiple comorbidities might depend on the hospital setting. As comorbidities usually are not uniformly collected and defined among different studies, comparison of the proportion of patients with comorbidities is difficult. Lastly, Switzerland has one of the most developed healthcare systems worldwide with one of the highest life expectancies (81.9 years for men and 85.9 years for women in 2019 [18]). Hence, hospitalised patients may have encountered COVID-19 disease in a generally better health status. In addition, staffing by well-educated nurses with a relatively high nurse to patient ratio was possible.

We observed a decline of the in-hospital mortality in the third wave, which might be due to the relative decrease of older patients – as mortality among older patients was the highest. The nationwide trends in Switzerland show a decline of the case fatality rate for COVID-19 patients (out- and inpatients) in all age groups (data derived from [13]). In the general population, this may be the result of increased testing, and thus more frequent detection of mild cases. However, the testing strategy for symptomatic patients has not changed in our hospital and systematic in-hospital screenings of asymptomatic patients – albeit

Figure 2: Proportion of patients during the three waves stratified by age (A), number of comorbidities (B), need for ICU (C), age at ICU (D) need for renal replacement therapy during hospital stay (E) and mortality (F). ICU = intensive care unit; RRT = renal replacement therapy.



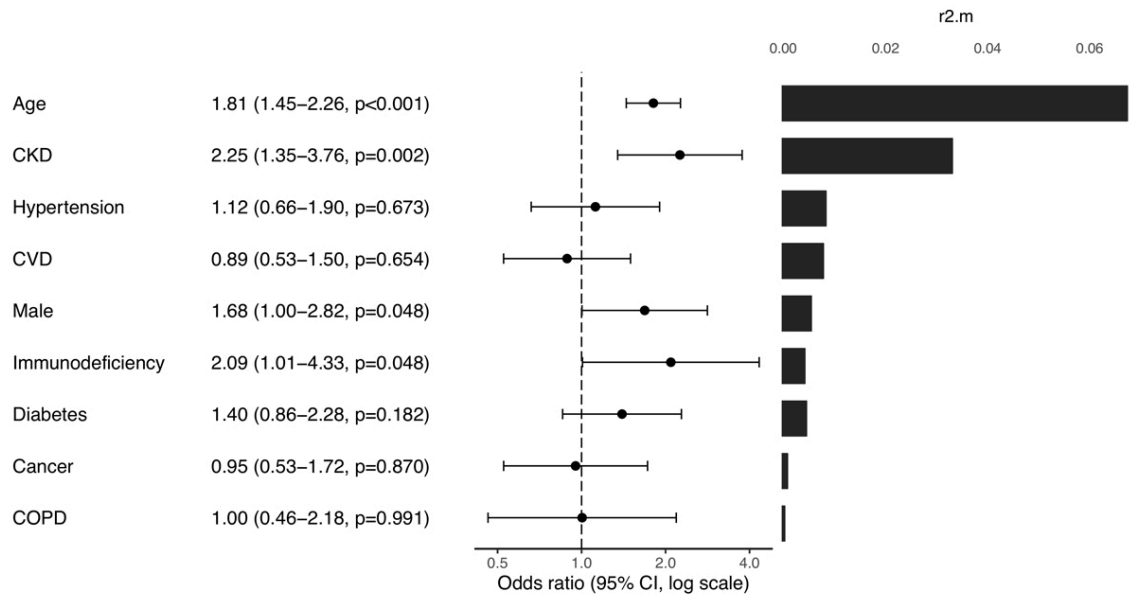
increased over time – detected a very small number of asymptomatic cases, not explaining the decrease of in-hospital-mortality [19]. The experience and evidence with the treatment of COVID-19 patients since the beginning of the pandemic have increased tremendously, both on the scientific international level and on the local institutional level [20], and might have impacted mortality. This might also be mirrored by the longer days on ICU of deceased patients seen in our study. Antiviral [21–23] and immunomodulatory treatments [24–28], as well as ventilation management [29, 30], might have affected mortality over time. On the other hand, changes in admission practices may also have influenced in-hospital mortality over time. The mortality in this study was lower than in comparable international studies, but still very considerable. Unfortunately, the small numbers and the retrospective nature of the study do not allow analysis of the effect of different treatments.

Table 2: Baseline characteristics of all patients and stratified by each wave, and survivors and patients who died.

	Surviving				Died			
	Overall	1st wave	2nd wave	3rd wave	Overall	1st wave	2nd wave	3rd wave
	n = 855 (91%)	n = 171 (90%)	n = 544 (90%)	n = 141 (95%)	n = 88 (9%)	n = 18 (10%)	n = 62 (10%)	n = 8 (5%)
Age (years), median (IQR)	63 (52–75)	60 (46–72)	66 (56–76)	56 (47–69)	75 (68–83)	75 (68–84)	76 (70–84)	69 (68–75)
Age group, n (%)								
– <50 years	180 (21)	53 (31)	84 (15)	43 (31)	3 (3)	0 (0)	3 (5)	0 (0)
– 50–64 years	276 (32)	49 (29)	171 (31)	56 (40)	8 (9)	2 (11)	6 (10)	0 (0)
– 65–79 years	274 (32)	54 (32)	189 (35)	31 (22)	43 (49)	9 (50)	28 (45)	6 (75)
– ≥80 years	125 (15)	15 (9)	100 (18)	10 (7)	34 (39)	7 (39)	25 (40)	2 (25)
Male sex, n (%)	533 (62)	104 (61)	346 (64)	83 (59)	63 (72)	11 (61)	47 (76)	5 (62)
Hospitalisation (days), median (IQR)	7 (5–13)	7 (4–12)	7 (5–13)	7 (4–11)	11 (5–18)	5 (3–10)	12 (6–18)	16 (5–24)
ICU admission, n (%)	148 (17)	30 (18)	95 (17)	23 (16)	58 (66)	9 (50)	42 (68)	7 (88)
Days in ICU, median (IQR)	8 (3–16)	10 (5–20)	7 (3–16)	7 (3–21)	10 (4–19)	6 (2–12)	10 (5–18)	20 (7–24)
COPD, n (%)	55 (6)	5 (3)	44 (8)	6 (4)	9 (10)	1 (6)	8 (13)	0 (0)
Diabetes, n (%)	230 (27)	31 (18)	170 (31)	29 (21)	35 (40)	4 (22)	29 (47)	2 (25)
Arterial hypertension, n (%)	388 (45)	72 (42)	260 (48)	56 (40)	59 (67)	15 (83)	39 (63)	5 (62)
Cardiovascular disease, n (%)	276 (32)	36 (21)	217 (40)	23 (16)	47 (53)	11 (61)	34 (55)	2 (25)
Immunocompromising condition, n (%)	90 (11)	23 (13)	51 (9)	16 (11)	13 (15)	2 (11)	10 (16)	1 (12)
Cancer, n (%)	140 (16)	29 (17)	99 (18)	13 (9)	20 (23)	4 (22)	15 (24)	1 (12)
Chronic kidney disease, n (%)	127 (15)	22 (13)	88 (16)	17 (12)	38 (43)	8 (44)	28 (45)	2 (25)
Renal replacement therapy during hospitalisation, n (%)	8 (1)	6 (4)	2 (0)	0 (0)	8 (9)	5 (28)	2 (3)	1 (12)
Days on RRT, median (IQR)	8 (3–15)	12 (7–17)	2 (2–6)	–	6 (1–14)	1 (1–12)	6 (4–12)	14 (14–14)

ICU = intensive care unit; COPD = chronic obstructive pulmonary disease; RRT = renal replacement therapy and was defined as renal replacement therapy during hospitalisation. The first wave was defined from 27 February to 30 June 2020, the second from 01 July 2020 to 28 February 2021 and the third from 01 March to 10 May 2021. Values are number (percentage) or median (interquartile range [IQR]).

Figure 3: Odds ratio plot displaying the adjusted odds ratio (OR) with the 95% confidence interval (CI) of each variable to predict in-hospital mortality over all three waves. On the right side the average contribution of each variable is plotted on a horizontal scale representing the average contribution of each variable to the model using McFadden R. A table with all the crude and fully adjusted effect estimates, 95% CI and p-values is presented in the appendix. CKD = chronic kidney disease; CVD = cardiovascular disease



In previous studies, infection with the variant B.1.1.7 has been linked to greater disease severity and possibly mortality [6, 7]. Since the beginning of March 2021, B.1.1.7 is considered the predominant variant in Switzerland, responsible for >90% of SARS-CoV-2 infections [13]. Although sequencing data for the patient population studied was not available, high rates of infection with B.1.1.7 can be assumed for the third wave in our patient population. Despite that, we did not observe an increase, but rather a decrease, in in-hospital mortality.

Interestingly, the duration of hospitalisation needed by survivors was similar across the different waves. However, as the follow-up in our study was limited to the hospitalisation period, it might not be a very good parameter for the duration of symptoms.

Acute kidney injury has been shown to be common among patients with COVID-19 [31–33] and occurring with a higher incidence in patients with COVID-19 than with other respiratory infections. Interestingly, over the course of the pandemic the need for renal replacement, as a surrogate for severe acute kidney injury therapy, decreased in our study. Given the high mortality of COVID-19-associated acute kidney injury, this is an encouraging finding and has been reported previously from the United States [34, 35]. The reasons for this decline are not quite clear, but implicate a change in clinical care, fluid administrations and a shift in demographics of the admitted patients.

Our study builds on the increasing evidence that chronic kidney disease, age, male sex and immunosuppressive conditions are important risk factors for in-hospital mortality [9, 10, 36, 37] and adds to the growing evidence that chronic kidney disease is a strong risk factor for in-hospital mortality [9, 10, 36, 37]. It highlights the importance of infection prevention in this vulnerable group of patients. Interestingly, we were able to show in our cohort that patients without comorbidities, regardless of their age, have a very low in-hospital mortality.

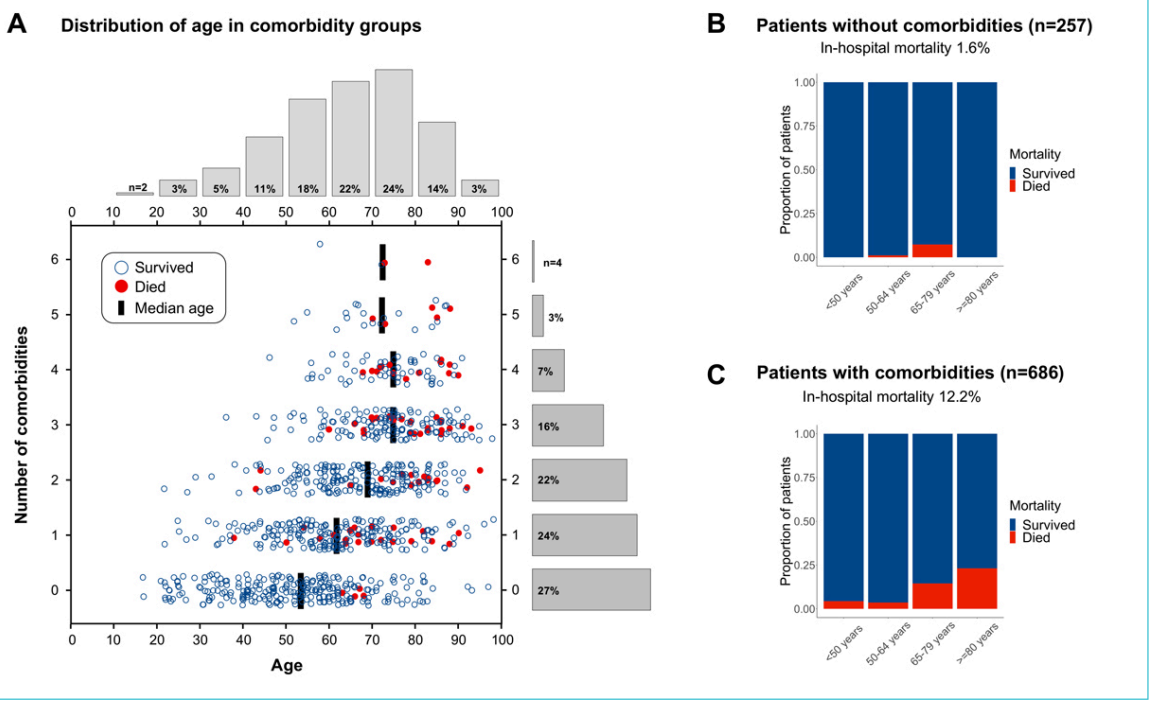
Our study has several limitations: This study was conducted at a single centre; thus, our findings might not be generalisable to other patient populations. Because of the retrospective nature of our study, not all parameters of interest were available for all patients (e.g., BMI) and might be subject to documentation bias. Comorbidities were recorded as assessed by the treating physician – the classification of comorbidities is therefore not consistent. In particular, in the absence of baseline values we defined chronic kidney disease as an eGFR <60ml/min/1.73m^2 that was not presumed to be a cause of unrecovered acute kidney injury. This might have led to an overrepresentation of chronic kidney disease if patients did not recover from acute kidney injury. However, this has been a limitation in most studies on this topic. We studied only all-cause mortality and therefore cannot exclude that patients died due to other causes.

The strength of our study is the analysis over the entire time span including three COVID-19 waves, the detailed knowledge on comorbidities and that across all waves all units involved adhered to standardised protocols. Hence, we could analyse all patients treated in our centre since the beginning of the pandemic and therefore provide a realistic picture of the development over time.

Conclusions

In our study overall in-hospital-mortality was 9.3%. Despite tremendous research efforts since the onset of the pandemic, in-hospital-mortality remained high. However, patients without comorbidities had a very low in-hospital mortality regardless of their age.

Figure 4: Mortality stratified by patients with and without comorbidities. Panel A shows a scatter plot with the circle representing all patients stratified by age and number of comorbidities. Blue circles represent survivors and red circles represent patients who died during the hospitalisation. Panels B and C report the proportion of in-hospital mortality in patients without any (B) and with any (C) comorbidities stratified by age.



Standardised, promptly adapted treatment protocols of all involved units and close collaboration supported the care of patients. Our study highlights the importance of infection prevention and control, and in particular, the vaccination campaigns.

Availability of data

Supporting information has been submitted as a separate file. Original data will be made available to the public upon publication.

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Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

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Appendix

Table of contents

STROBE statement

Supplemental table S1 STROBE Statement Checklist			
	Item No	**Recommendation**	**Provided on page**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-7
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7, Figure S2
		(b) Give reasons for non-participation at each stage	Figure S2
		(c) Consider use of a flow diagram	Figure S2
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9, Table 1 and 2
		(b) Indicate number of participants with missing data for each variable of interest	Table S1
		(c) Summarise follow-up time (eg, average and total amount)	NA

Outcome data	15	Report numbers of outcome events or summary measures over time	7-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table S2
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

Statistical supplement

List of used R packages:

- readxl
- finalfit
- dplyr
- ggplot2
- tidyr
- tableone
- tibble
- openxlsx
- rstatix
- summarytools
- ggsci
- ggpubr
- dominanceanalysis

Model performance

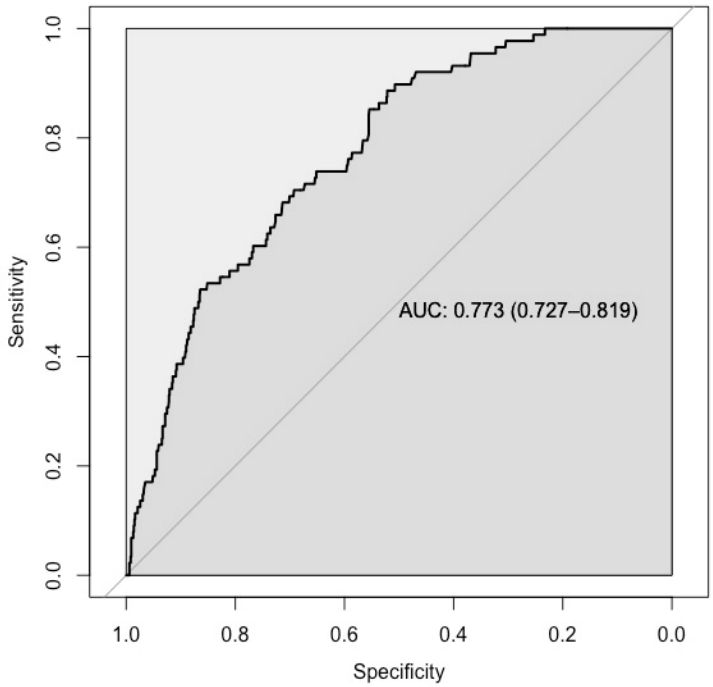


Figure S1 Receiver operator characteristics curve displaying the area under the curve (AUC) and the 95% confidence interval for the logistic regression model predicting in-hospital mortality in patients with COVID-19.

Missing values

Supplemental table S1 Missing values. BMI denotes body mass index, COPD denotes chronic obstructive pulmonary disease; CKD denotes chronic kidney disease, RRT denotes. * BMI was not included in the analysis due to missing values.

Variable	Total N	Missing N
Age	943	0
Sex	943	0
BMI *	943	454
Intensive Care	943	0
COPD	943	0
Diabetes	943	0
Hypertension	943	0
Cardiovascular disease	943	0
Immunocompromising condition	943	0
Cancer	943	0
CKD	943	0
RRT	943	0

Study flowchart

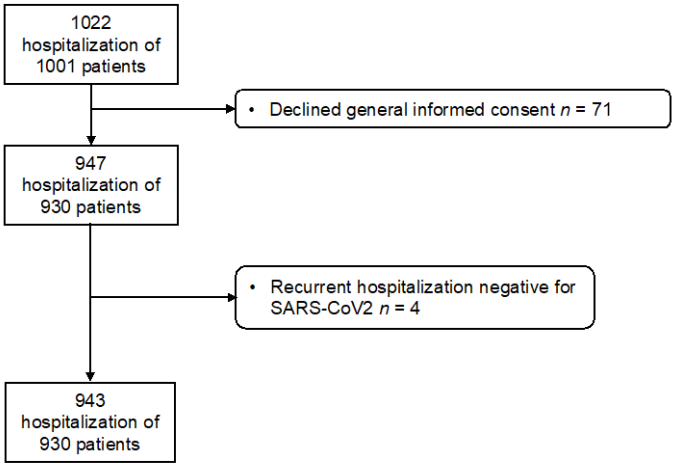
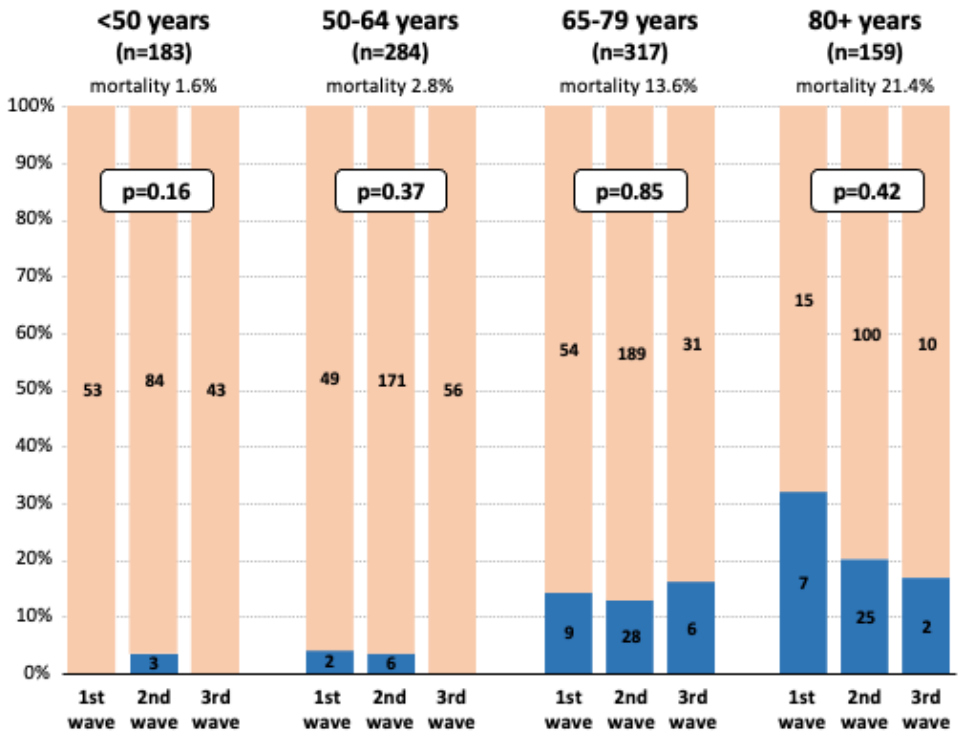


Figure S2 Study flowchart of the study population.

Additional figures



Supplemental figure S3. Mortality of each wave stratified by the age group.

Additional tables

Table S2: Factors associated with Mortality from logistic regression modeling. CKD denotes chronic kidney disease, COPD denotes chronic obstructive pulmonary disease, OR denotes odds ratio and is displayed as OR (95% confidence interval).

	Survived	**Died**	**OR (univariable)**	**OR (multivariable)**
Male Sex	533 (89.4)	63 (10.6)	1.52 (0.94-2.47, p=0.088)	1.68 (1.00-2.82, p=0.048)
Age, Mean (SD)	62.5 (16.2)	75.0 (11.3)	1.84 (1.54-2.21, p<0.001)	1.81 (1.45-2.26, p<0.001)
Diabetes	230 (86.8)	35 (13.2)	1.79 (1.14-2.82, p=0.011)	1.40 (0.86-2.28, p=0.182)
Hypertension	388 (86.8)	59 (13.2)	2.45 (1.54-3.90, p<0.001)	1.12 (0.66-1.90, p=0.673)
Cardiovascular disease	276 (85.4)	47 (14.6)	2.40 (1.54-3.74, p<0.001)	0.89 (0.53-1.50, p=0.654)
Immunocompromising condition	90 (87.4)	13 (12.6)	1.47 (0.79-2.76, p=0.227)	2.09 (1.01-4.33, p=0.048)
CKD	127 (77.0)	38 (23.0)	4.36 (2.74-6.91, p<0.001)	2.25 (1.35-3.76, p=0.002)
Cancer	140 (87.5)	20 (12.5)	1.50 (0.88-2.55, p=0.133)	0.95 (0.53-1.72, p=0.870)
COPD	55 (85.9)	9 (14.1)	1.66 (0.79-3.48, p=0.182)	1.00 (0.46-2.18, p=0.991)