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Swiss COVID-19 hospital surveillance: an in-depth analysis of the factors associated with hospital readmission dynamics in community-acquired COVID-19 cases

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Summary

BACKGROUND: The COVID-19 pandemic has placed unprecedented pressure on hospitals worldwide. In such a context of tension in healthcare systems, efficiently allocating hospital resources is a crucial aspect of crisis management. The aim of this study was to describe the clinical characteristics of readmitted patients and to determine risk factors for hospital readmission using data from the Swiss COVID-19 Hospital-Based Surveillance system (CH-SUR).

METHODS: We investigated hospital readmissions within 60 days after discharge of patients from the CH-SUR surveillance system with a first hospitalisation between 1 December 2020 and 1 December 2021. Only community-acquired cases were considered. We compared the baseline characteristics of readmitted and non-readmitted patients. We performed univariable and multivariable logistic regression analyses to investigate the risk factors for hospital readmission.

FINDINGS: Of the 8039 eligible patients, 239 (3.0%, 95% confidence interval [CI] 2.6–3.3%) were readmitted to hospital within 60 days of discharge, with no significant variations observed over the study period; 80% of all readmissions occurred within 10 days of discharge of the index hospital stay. Based on our multivariable logistic regression models, factors increasing the odds of hospital readmission were age ≥65 years (odds ratio [OR] 1.63, 95% CI 1.24–2.15), male sex (OR 1.47, 95% CI 1.12–1.93), being discharged to home after first hospitalisation (OR 1.77, 95% CI 1.19–2.62), having oncological pathology (OR 1.82, 95% CI 1.27–2.61) and being immunosuppressed (OR 2.34, 95% CI 1.67–3.29).

INTERPRETATIONS: Age, sex, cardiovascular diseases, oncological pathologies and immunosuppression were the main risk factors identified for hospital readmission.

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Introduction

The 2019 coronavirus disease (COVID-19) has placed unprecedented burdens on acute care systems. The pandemic highlighted the importance of efficiently allocating hospital beds and resources to manage the overwhelming COVID-19 hospitalisation rate, as high as 32 hospitalisations per 100,000 cases in the United States [1] and 6 hospitalisations in 100,000 cases in Switzerland [2]. Discharging recovered COVID-19 patients in a timely manner is important for maximising healthcare capacity and preventing unnecessary morbidity and mortality from overburdened hospitals [3]. There is, however, a risk of hastily discharging patients who have not fully recovered, which may result in hospital readmission [4]. Hospital readmis-

sion of COVID-19 patients is unfortunately not rare, which constitutes a substantial public health concern [5] as it relates to patient safety and hospital resources. Discharging COVID-19 patients is a delicate balancing act that requires a detailed understanding of patients' clinical course and the trajectory of their readmission risk after discharge.

The majority of published studies on COVID-19 hospital readmission have been conducted with data from small hospitals [6–12]. The low numbers of readmissions recorded in these studies (often below 100) limits analyses on potential risk factors for readmission. However, a few notable large-sample readmission studies have been conducted, and they have typically found that the factors associated with high readmission odds are the same as those associated with severe COVID-19. The US CDC study, which analysed 9504 readmissions (9% readmission rate) over a 60-day follow-up, found increased odds of readmission for patients aged 65 and over, patients discharged to a long-term care facility, patients with one of the five comorbidities chronic obstructive pulmonary disease, heart failure, diabetes, chronic kidney disease and obesity [13]. A study from South Korea of 328 readmissions out of 7590 discharges (4% readmission rate) found a higher readmission rate for men, older individuals and patients with a high Charlson Comorbidity Index score [14].

Such findings, however, may not be generalisable to patients in other countries with different demographics and healthcare systems. Additional analyses of large cohorts of discharged COVID-19 patients are therefore valuable. Switzerland has a comprehensive database of COVID-19 hospital admissions and readmissions from several large secondary (cantonal) and tertiary (university) hospitals.

Understanding the association between COVID-19 disease courses and readmissions is impactful for policy making to optimise healthcare delivery. The aim of this study was to describe the demographic and clinical characteristics of patients with COVID-19 who were readmitted and to determine the risk factors for hospital readmission, with the underlying goal of providing valuable information to reduce the risk of readmission and improve patient management. If patients with certain demographic or clinical characteristics are at higher risk of readmission, these patients may be targeted for a delayed discharge and proper outpatient follow-up. Derived algorithms may reduce morbidity by supporting the rapid identification of deteriorating patients and the coordination of appropriate care interventions [15].

Study design and statistical methods

Data source

COVID-19 Hospital-Based Surveillance (CH-SUR) is a prospective surveillance system for COVID-19 and influenza coordinated by the Swiss Federal Office of Public Health (FOPH) and the Institute of Global Health (ISG) of the University of Geneva [16, 17]. First established in 2018 to capture influenza-related hospitalisations, it was adapted in March 2020 to collect detailed information on COVID-19 hospitalised patients in Switzerland, at the national scale. It includes paediatric and adult patients hospitalised for more than 24 hours and diagnosed with COVID-19 confirmed by a laboratory test (e.g. polymerase chain reaction [PCR]), and in addition probable cases with serology or with a computed tomography (CT) scan and chest X-ray compatible with a COVID-19 diagnosis. Up to 21 hospitals throughout Switzerland have been participating in this surveillance. CH-SUR was proven to capture a large proportion of the hospitalisations related to COVID-19 in Switzerland, ensuring its overall representativeness of the COVID-19 situation in the country [2, 16, 18].

CH-SUR registers information on demographics, admission, clinical context (including comorbidities, complications, admission to intermediate care unit [IMCU] and/or intensive care unit [ICU] and treatments) and follow-up (death, discharge or transfer), for each hospitalisation related to COVID-19 recorded in the system. Patients who experienced multiple hospitalisations within the hospitals participating in the surveillance are appropriately identified, making it possible to follow their course within hospitals participating in CH-SUR.

For the analysis, we included all CH-SUR adult patients aged 18 years or over hospitalised for the first time between 23 December 2020 and 20 December 2021, and who were discharged after their first (and possibly only) hospitalisation. Given that definitions and collected variables have evolved over time, we selected this time interval because (a) both the collected variables and database were stable and (b) it coincides with the time period from the introduction of vaccination to the emergence of the Omicron variant. The first hospitalisation of the included patients was considered the index hospitalisation. In the data collection form, hospitals are able to specify whether a patient died after discharge (in the event that they are informed about this). However, no systematic patient follow-up is carried out.

Of the 21 hospitals participating in the CH-SUR surveillance programme over that period of time, one was excluded from the analysis due to data completeness issues and 6 paediatric centres with no adult cases were excluded. Consequently, the data we used was collected from 14 hospitals.

The study was submitted and approved by the Geneva Ethics Committee (CCER) and by all hospitals' local Ethics Committees through the Swiss ethics BASEC submission system, under reference 2020-00827.

Statistical analysis

We investigated hospital readmissions within 60 days after discharge of the index hospitalisation in the CH-SUR system. Readmission was defined as an admission of a previously discharged patient due to COVID-19 within 60 days of the last discharge date. We limited our analysis to the patients for whom the outcome of the index hospitalisation was documented, and who survived (as far as documented) their index hospitalisation. We excluded patients transferred to a hospital not participating in CH-SUR, which can be considered as "lost to follow up" since their outcome will remain unknown. We also excluded patients with missing age or sex, as well as patients classified as nosocomial SARS-CoV-2 infections during their index hospitalisation.

All analyses were conducted in R (version 4.2.1). First, we compared the baseline characteristics of readmitted and

non-readmitted patients, via Chi-squared tests for categorical variables. Then, we calculated cumulative incidence functions (CIFs) for hospital readmission, overall and stratified by variables, using the R package *mstate* [19]. We also present descriptive statistics of the conditions and events during the second hospitalisation among the patients who were readmitted within 60 days of first discharge.

We used univariable and multivariable logistic regression to investigate the risk factors for hospital readmission within 60 days after discharge. We considered the following variables in the univariable model: age (<65 vs ≥65 years), sex, discharge to home (versus other facility/long-term care), IMCU/ICU stay, COVID-19 immunisation status (fully, partially or not immunised), diabetes, hypertension, cardiovascular disease, renal disease, oncological pathology, obesity, respiratory disease, immunosuppression, or receiving any treatment. All variables refer to the index hospitalisation and were recorded dichotomously (yes/no) unless otherwise mentioned. These covariables were preselected based on suspected clinical relevance and stratum sizes. Of comorbidities, only those with at least 8% prevalence in the database were considered. Detailed definitions of some of these covariables can be found in Appendix A.1 and the latest version of the variable description is also available on the CH-SUR website (https://www.unige.ch/medecine/hospital-covid/).

We selected the variables to be included in the multivariable analysis using the Akaike Information Criterion (AIC) and Sawa's Bayesian Information Criterion (SBIC). The model with the lowest value for AIC and SBIC including at least age, sex, discharge to home and IMCU/ICU attendance was selected. If the results of AIC and SBIC differed, the model with the higher number of variables was selected.

We imputed missing values of all other covariables using multiple imputation by chained equation (R package *mice* [20]). To improve the results of the imputation, we added the outcome and the name of the hospital of index admission into the imputation equation. We ran each model on 20 imputed datasets, and combined the estimates with Rubin's rule [20]. Complete case analyses with univariable and multivariable models were conducted as sensitivity analyses.

To assess the robustness of our results, we recalculated multivariable logistic regression models without multiple imputation, excluding all patients with incomplete information on any of the adjusted covariables. Multivariable analyses stratified by age (<65 vs ≥65 years) were performed to investigate the interaction of age with other covariables. We also compared the case fatality ratios between the index hospitalisation and rehospitalisation using proportion testing. In this analysis, patients who died during the index hospitalisation but otherwise fulfilled the inclusion criteria were also included. Finally, a comparison of respiratory disease severity using the CURB-65 score between the index hospitalisation and the rehospitalisation was performed in patients who were readmitted and developed respiratory symptoms during their second hospitalisation.

We investigated the possible collinearities between the explanatory variables of the multivariable logistic regression model, via pairwise Chi-squared tests, and evaluated the consequences it could have on the robustness of results.

Results

A total of 11,231 COVID-19 hospitalised patients were reported in CH-SUR between 23 December 2020 and 20 December 2021. None of the patients had a missing age, but we excluded two patients with missing sex and 1235 patients registered as nosocomial SARS-CoV-2 infection at index hospitalisation. Among the 9994 remaining patients, for 604 (6.0%) the outcome of index hospitalisation was unknown, 912 (9.1%) died during their index hospitalisation, 56 (0.6%) died after being discharged from their index hospitalisation and 368 (3.7%) were transferred outside the CH-SUR system; these patients were excluded from the analyses. The remaining 8039 patients left the hospital alive at the end of the index hospitalisation.

Characteristics of COVID-19 patients

Out of the 8039 hospitalised patients included in our analyses, 239 (3.0%, 95% CI 2.6–3.3%) were readmitted within 60 days after discharge of the index hospitalisation. Slightly less than half of the patients were aged above 65 years (n = 3628, 45.1%) and 908 patients (11.3%) had been fully vaccinated by the time of admission. Most patients had at least one complication (n = 6500, 80.9%).

The CH-SUR hospital readmission rate over time is presented in figure 1. It varied between 1.6% (95% CI 0.0–3.8%) (June 2021) and 4.6% (95% CI 3.2–6.1%) (November 2021).

The characteristics of patients, overall and stratified per readmission status, are detailed in table 1.

Further descriptive characteristics specific to the group of readmitted patients are given in table 2.

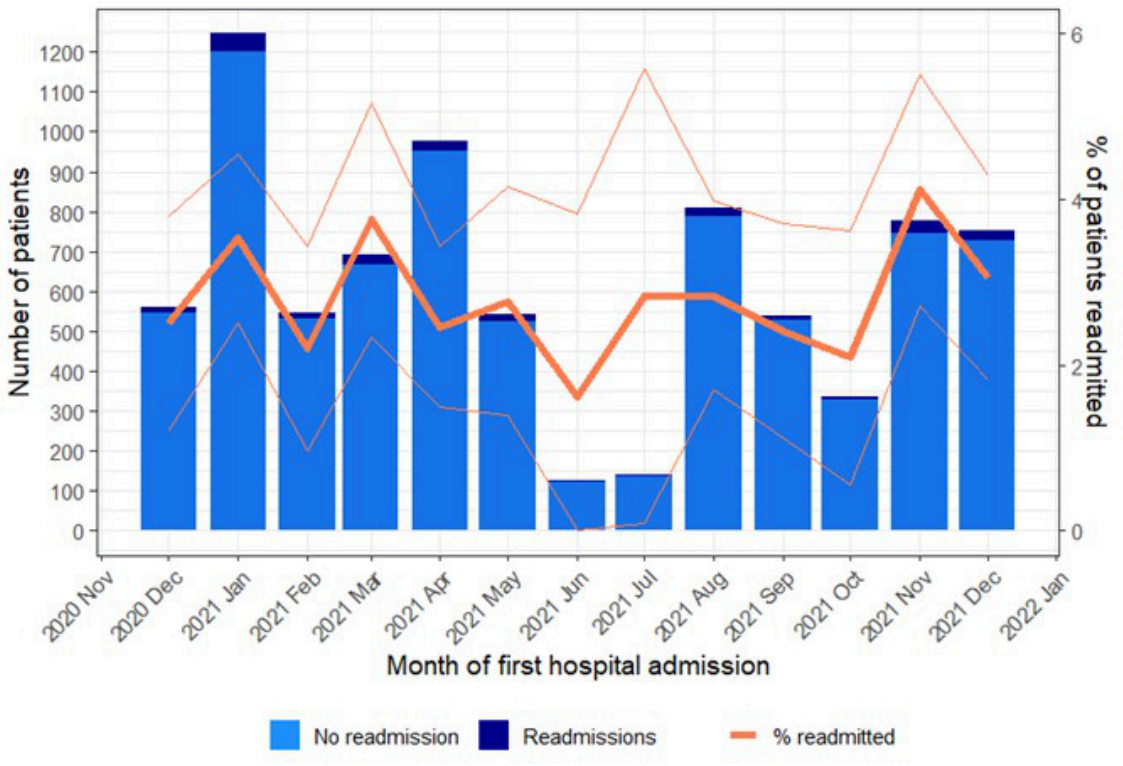
Figure 2 shows the overall cumulative incidence functions of readmission. Stratified cumulative incidence functions of readmission within 60 days can be found in Appendix A.2. Overall, 50% of the readmissions occurred within four days and 80% of the readmissions within ten days after index discharge.

Figure 3 shows the distribution of time to hospital readmission, stratified per index hospitalisation duration. Among the readmitted patients, the median time to readmission was shorter for those with an index hospitalisation duration of <5 days (median of 3 days, IQR 2–4 days) than for those with an index hospitalisation duration of 5 days or longer.

Overall 17.2% of the readmitted patients spent time in the IMCU/ICU during the subsequent hospitalisation, compared to 16.6% for the index hospitalisations among all patients. In total, 87.0% of the readmitted patients showed at least one complication during the readmission stay, and the most common complications were: respiratory complications (63.2%), deconditioning syndrome (21.3%) and thrombosis complications (13.4%) (table 2). The case fatality ratio was 9.2% (95% CI 8.6–9.7%) during the index hospitalisation and 7.1% (95% CI 3.9–10.4%) during rehospitalisation (p = 0.72).

Among the 151 patients who were readmitted and had respiratory complications at readmission, 95 (62.9%) had the same CURB-65 score at the index hospitalisation and at

Figure 1: Time trends of hospital readmission in CH-SUR. The figure shows the absolute counts of hospitalisations and readmissions on the left scale, and the percentage of readmissions on the right scale, by month of index hospitalisation. The orange line demonstrates the proportion of patients with index hospitalisation in a given month who were subsequently readmitted within 60 days after their discharge.



readmission, 37 (24.5%) had a higher CURB-65 score at readmission and 19 (12.6%) had a lower CURB-65 score at readmission (figure 4).

Risk factors for hospital readmission within CH-SUR

Table 3 shows the odds ratios (ORs) for hospital readmission within 60 days in CH-SUR, with 95% confidence intervals (95% CIs), from the univariable logistic regression.

The model with the same eight covariables (oncological pathology, obesity, immunosuppression and any treatment, in addition to age, sex, discharge to home and ICU/IMCU stay) produced the lowest values for both AIC and SBIC and was therefore selected for the multivariable analysis. Table 4 shows the ORs and 95% CIs for hospital readmission within 60 days, from the multivariable logistic regression models using either the imputed dataset or the complete cases dataset. Of note, when limiting to cases with complete follow-up information in the multivariable analysis, the number of included patients dropped from 8039 to 5161, with 163 (3.2%) readmissions within 60 days after discharge of index hospitalisation.

Based on our multivariable logistic regression models, factors increasing the odds of hospital readmission were age of 65 years or older (OR 1.63, 95% CI 1.24–2.15, p <0.001), being discharged to home at the end of the index hospitalisation (OR 1.77, 95% CI 1.19–2.62, p = 0.004),

Figure 2: Cumulative incidence function for hospital readmission – overall.

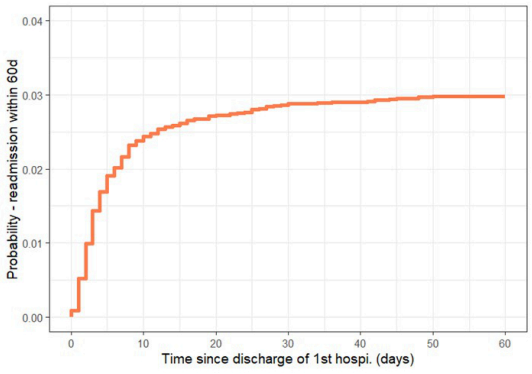


Figure 3: Time to hospital readmission as a function of the duration of the index hospitalisation. The shape of each plot presents the frequency of patients with a given number of days between the discharge and rehospitalisation; the box shows the median and interquartile range. Numbers in orange at the top of the figure are the number of patients readmitted for the considered index duration.

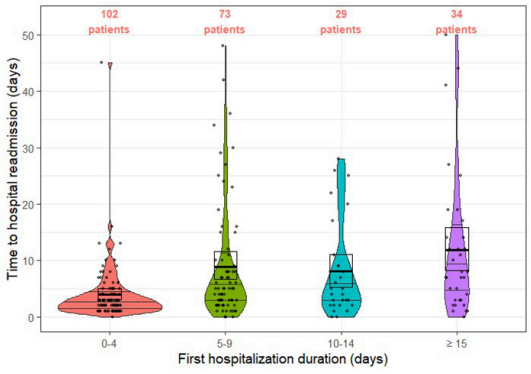


Table 1:
Characteristics of all patients included in the analysis, of patients not readmitted and patients readmitted within 60 days. P-values from Chi-squared tests compare the distributions of variables between these two groups.

		All (n = 8039)	Non-readmitted (n = 7800)	Readmitted (n = 239)
Age (years)	<65	4411 (54.9%)	4310 (55.3%)	101 (42.3%)
	≥65	3628 (45.1%)	3490 (44.7%)	138 (57.7%)
Sex	Male	4385 (54.5%)	4233 (54.3%)	152 (63.6%)
	Female	3654 (45.5%)	3567 (45.7%)	87 (36.4%)
Discharged to home for index hospitalisation	Yes	6311 (78.5%)	6106 (78.3%)	205 (85.8%)
	No	1675 (20.8%)	1643 (21.1%)	32 (13.4%)
	Unknown	53 (0.7%)	51 (0.7%)	2 (0.8%)
Origin for index hospitalisation	Home	7379 (91.8%)	7161 (91.8%)	218 (91.2%)
	Long-term care	129 (1.6%)	123 (1.6%)	6 (2.5%)
	Other hospital	374 (4.7%)	367 (4.7%)	7 (2.9%)
	Other	157 (2.0%)	149 (1.9%)	8 (3.3%)
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)
Any IMCU/ICU stay during index hospitalisation	Yes	1337 (16.6%)	1314 (16.8%)	23 (9.6%)
	No	6685 (83.2%)	6469 (82.9%)	216 (90.4%)
	Unknown	17 (0.2%)	17 (0.2%)	0 (0.0%)
COVID-19 immune status (at index hospitalisation)*	Fully immunised	908 (11.3%)	869 (11.1%)	39 (16.3%)
	Not immunised	5810 (72.3%)	5647 (72.4%)	163 (68.2%)
	Partially immunised	284 (3.5%)	275 (3.5%)	9 (3.8%)
	Unknown	1037 (12.9%)	1009 (12.9%)	28 (11.7%)
Diabetes	Yes	1615 (20.1%)	1568 (20.1%)	47 (19.7%)
	No	6405 (79.7%)	6213 (79.7%)	192 (80.3%)
	Unknown	19 (0.2%)	19 (0.2%)	0 (0.0%)
Hypertension	Yes	3381 (42.1%)	3267 (41.9%)	114 (47.7%)
	No	4632 (57.6%)	4508 (57.8%)	124 (51.9%)
	Unknown	26 (0.3%)	25 (0.3%)	1 (0.4%)
Cardiovascular disease	Yes	1940 (24.1%)	1857 (23.8%)	83 (34.7%)
	No	6071 (75.5%)	5916 (75.8%)	155 (64.9%)
	Unknown	28 (0.3%)	27 (0.3%)	1 (0.4%)
Renal disease	Yes	1048 (13.0%)	1004 (12.9%)	44 (18.4%)
	No	6961 (86.6%)	6767 (86.8%)	194 (81.2%)
	Unknown	30 (0.4%)	29 (0.4%)	1 (0.4%)
Oncological pathology	Yes	688 (8.6%)	645 (8.3%)	43 (18.0%)
	No	7311 (90.9%)	7119 (91.3%)	192 (80.3%)
	Unknown	40 (0.5%)	36 (0.5%)	4 (1.7%)
Obesity (body mass index ≥30 kg/m^2)	Yes	2212 (27.5%)	2155 (27.6%)	57 (23.8%)
	No	4499 (56.0%)	4341 (55.7%)	158 (66.1%)
	Unknown	1328 (16.5%)	1304 (16.7%)	24 (10.0%)
Respiratory disease	Yes	1266 (15.7%)	1214 (15.6%)	52 (21.8%)
	No	6742 (83.9%)	6555 (84.0%)	187 (78.2%)
	Unknown	31 (0.4%)	31 (0.4%)	0 (0.0%)
Immunosuppression**	Yes	695 (8.6%)	648 (8.3%)	47 (19.7%)
	No	7313 (91.0%)	7121 (91.3%)	192 (80.3%)
	Unknown	31 (0.4%)	31 (0.4%)	0 (0.0%)
Any treatment (at index hospitalisation)***	Yes	5139 (63.9%)	4994 (64.0%)	145 (60.7%)
	No	1140 (14.2%)	1099 (14.1%)	41 (17.2%)
	Unknown	1760 (21.9%)	1707 (21.9%)	53 (22.2%)
Any complication (at index hospitalisation)	Yes	6500 (80.9%)	6310 (80.9%)	190 (79.5%)
	No	1500 (18.7%)	1451 (18.6%)	49 (20.5%)
	Unknown	39 (0.5%)	39 (0.5%)	0 (0.0%)

ICU: intensive care unit; IMCU: intermediate care unit.

*Full immunisation corresponds to having received all required doses of a vaccine or at least one dose + documented prior SARS-CoV-2 infection. Partial immunisation means having received one dose of a vaccine other than Janssen's.

**Immunosuppression includes patients who have a haematological, rheumatological or autoimmune pathology with immunosuppression, who receive immunosuppressive treatment, or who are HIV-infected.

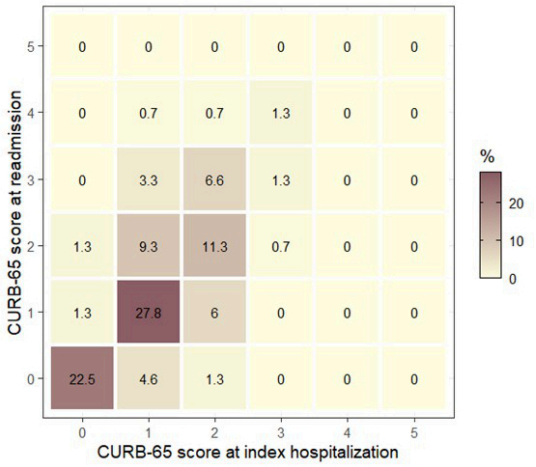
***Includes antiviral treatment, antibody treatment and corticosteroid treatment.

Further details of the variable definitions are provided in Appendix A.1.

presence of oncological pathology (OR 1.82, 95% CI 1.27–2.61, p = 0.001) and immunosuppression (OR 2.34, 95% CI 1.67–3.29, p <0.00001). Females had lower odds of hospital readmission than males (OR 0.68, 95% CI 0.52–0.89, p = 0.005). Being admitted at least once to the IMCU/ICU during the index hospitalisation, obesity and receiving any treatment during the index hospitalisation

were found to have no significant impact on the risk of hospital readmission.

Figure 4: Comparison of the severity scores at index hospitalisation and at readmission, for the patients readmitted with respiratory complications (n = 151).



The collinearity check revealed some collinearity particularly between age and other variables, but the results of the model omitting age did not essentially differ from those of the main analysis (Appendix A.3). We also conducted an analysis stratified by age (<65 vs ≥65 years) to test whether the lower readmission rate among patients who stayed at the IMCU or ICU during the index hospitalisation could be related to the younger age of these patients. The odds ratios did however not essentially differ between the two age groups, although there were some minor differences: discharge was no longer significantly associated with rehospitalisation in the younger age group, and immunosuppression was not associated with rehospitalisation in the older age group (Appendix A.3).

Discussion

In this study using Swiss COVID-19 Hospital-Based Surveillance (CH-SUR) data, we assessed the risk of hospital readmission within 60 days among COVID-19 patients discharged alive from the hospital, and investigated the risk factors for hospital readmission. Between December 2020 and December 2021, the rate of hospital readmission within 60 days among COVID-19 patients was 3.2%, with

Table 2:
Characteristics at readmission among patients rehospitalised within 60 days of discharge.

Patient characteristics		**Readmitted (n = 239)**
Time from index discharge to readmission in days, median (interquartile range)		4 (2–8)
Outcome of readmission	Discharged	213 (89.1%)
	Transferred outside CH-SUR	1 (0.4%)
	Died	21 (8.8%)
	Incomplete data	4 (1.7%)
CURB-65 score at readmission	0	72 (30.1%)
	1	87 (36.4%)
	2	52 (21.8%)
	3+	28 (11.7%)
Any IMCU/ICU stay during readmission	Yes	41 (17.2%)
	No	197 (82.4%)
	Unknown	1 (0.4%)
Number of complications (at readmission)	0	29 (12.1%)
	1	71 (29.7%)
	2	65 (27.2%)
	3+	72 (30.1%)
	Unknown	2 (0.8%)
Respiratory complication (at readmission)	Yes	151 (63.2%)
	No	85 (35.6%)
	Unknown	3 (1.3%)
Deconditioning syndrome (at readmission)	Yes	51 (21.3%)
	No	184 (77%)
	Unknown	4 (1.7%)
Renal complication (at readmission)	Yes	31 (13%)
	No	205 (85.8%)
	Unknown	3 (1.3%)
Thrombosis complication (at readmission)	Yes	32 (13.4%)
	No	203 (84.9%)
	Unknown	4 (1.7%)
Bacterial complication (at readmission)	Yes	28 (11.7%)
	No	207 (86.6%)
	Unknown	4 (1.7%)
Any complication (at readmission)	Yes	208 (87.0%)
	No	29 (12.1%)
	Unknown	2 (0.8%)

ICU: intensive care unit; IMCU: intermediate care unit.

little variation observed over that time period (ranging from 1.6% to 4.6%).

Due to the growing recognition of COVID-19's medium- and long-term health consequences, there has been significant interest in studying the post-discharge trajectory of COVID-19 patients. Reported readmission rates range between 4% [21] and 9% [13] from large sample studies in Spain and the United States, respectively, with readmissions occurring typically within the first week post-discharge. Respiratory distress was identified as the most common reason for readmission [22]. Other reasons for readmission included: pain, altered mental status, fall, fever, soft tissue infection, thrombotic event and gastrointestinal symptoms [7, 21–25]. We observed lower readmis-

Table 3:
Odds ratios with 95% confidence intervals (95% CI) from univariable logistic regression.

Variable		Odds ratio (95% CI)	p-value
Age (years)	<65	1 (ref)	<0.0001
	≥65	1.69 (1.30–2.19)	
Sex	Male	1 (ref)	0.004
	Female	0.68 (0.52–0.89)	
Discharged to home for index hospitalisation	No	1 (ref)	0.003
	Yes	1.72 (1.18–2.51)	
Any IMCU/ICU stay during index hospitalisation	No	1 (ref)	0.002
	Yes	0.52 (0.34–0.81)	
COVID-19 immune status (at index hospitalisation)	Not immunised	1 (ref)	0.07
	Fully immunised	1.55 (1.09–2.22)	
	Partially immunised	1.13 (0.57–2.24)	
Diabetes	No	1 (ref)	0.85
	Yes	0.97 (0.70–1.34)	
Hypertension	No	1 (ref)	0.07
	Yes	1.27 (0.98–1.64)	
Cardiovascular disease	No	1 (ref)	0.0002
	Yes	1.71 (1.30–2.24)	
Renal disease	No	1 (ref)	0.02
	Yes	1.53 (1.09–2.13)	
Oncological pathology	No	1 (ref)	<0.00001
	Yes	2.47 (1.76–3.47)	
Obesity	No	1 (ref)	0.04
	Yes	0.73 (0.53–0.99)	
Respiratory disease	No	1 (ref)	0.01
	Yes	1.50 (1.10–2.05)	
Immunosuppression	No	1 (ref)	<0.00001
	Yes	2.69 (1.94–3.74)	
Any treatment (at index hospitalisation)	No	1 (ref)	0.17
	Yes	0.78 (0.55–1.11)	

ICU: intensive care unit; IMCU: intermediate care unit.

Please refer to table 1 and Appendix A.1 for a detailed explanation of the variables.

Table 4:
Odds ratios with 95% confidence intervals (95% CI) from multivariable logistic regression on imputed data (mice), and multivariable logistic regression on complete cases (cc).

		Multivariable (mice)		Multivariable (cc)	
Variable		**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Age (years)	<65	1 (ref)	0.0005	1 (ref)	0.0006
	≥65	1.63 (1.24–2.15)		1.55 (1.11–2.16)	
Sex	Male	1 (ref)	0.005	1 (ref)	0.06
	Female	0.68 (0.52–0.89)		0.75 (0.53–1.04)	
Discharged to home for index hospitalisation	No	1 (ref)	0.005	1 (ref)	0.002
	Yes	1.77 (1.19–2.62)		1.68 (1.08–2.69)	
Any IMCU/ICU stay during index hospitalisation	No	1 (ref)	0.08	1 (ref)	0.09
	Yes	0.67 (0.43–1.05)		0.74 (0.45–1.18)	
Oncological pathology	No	1 (ref)	0.001	1 (ref)	<0.00001
	Yes	1.82 (1.27–2.61)		2.11 (1.37–3.16)	
Obesity	No	1 (ref)	0.46	1 (ref)	0.04
	Yes	0.89 (0.65–1.22)		0.73 (0.50–1.04)	
Immunosuppression	No	1 (ref)	<0.00001	1 (ref)	0.001
	Yes	2.34 (1.67–3.29)		2.09 (1.36–3.12)	
Any treatment (at index hospitalisation)	No	1 (ref)	0.21	1 (ref)	0.34
	Yes	0.80 (0.56–1.14)		0.82 (0.56–1.24)	

ICU: intensive care unit; IMCU: intermediate care unit.

sion rates than those reported previously in a systematic review [26]. However, most of the studies included were based on data collected in 2020, during the first months of the COVID-19 pandemic, when the understanding of COVID-19 and its management were still limited. Case management of hospitalised patients drastically changed with the results of the first large clinical trials during summer 2020 and the broader use of immunomodulatory drugs in patients with severe disease [27]. The disease itself and its management evolved from the beginning of the pandemic. New variants of COVID-19 appeared and co-existed, changing disease severity. The vaccine policy kept evolving, with new vaccine doses being administered to preserve immunity, leading to a beneficial impact on recovery.

The time from index hospitalisation discharge to readmission was relatively short, with a median time of four days. This may indicate that hospital readmissions within CH-SUR generally occur early enough to avoid a severe degradation of the status of the patient. We found that most of the readmitted patients had similar severity scores at index admission and at readmission. The in-hospital case fatality ratio was found to be slightly lower, although not significantly, after hospital readmission than at the end of index hospitalisation. Post-discharge, this short time span between index hospitalisation discharge and readmission could justify short-term medical surveillance for at-risk patients (males, with comorbidities, older than 65) in order to identify as quickly as possible any complication which would require further hospitalisation.

As previously reported by others [13, 14, 28], male sex and age of 65 years or over were found to increase the risk of hospital readmission within CH-SUR. Differences in the effects of COVID-19 by sex and age have been evidenced by several studies, with older patients as well as male patients being generally associated with a worse outcome [18]. This unbalanced sex-associated risk could relate to the difference in immune response to the SARS-CoV-2 virus between men and women [29,30], but it could also be associated with the higher prevalence among men than women of chronic diseases known to be COVID-19 risk factors. Likewise, the elderly population is known to have a reduced immune response, and to more likely present comorbidities that are risk factors for COVID-19 adverse events [18].

Patients with chronic cardiovascular diseases as well as immunocompromised patients had a significantly higher risk of hospital readmission compared to those without such comorbidities. Similar results have been demonstrated in other studies [21,31]. Immunosuppression, as defined in CH-SUR and in other studies, encompasses a wide range of immune dysfunctions and the risk may vary within this group. It is particularly worth noting that our definition considered all HIV-infected individuals as immunocompromised, although at present most individuals diagnosed with HIV in Switzerland are virally suppressed and with good immunological response. The increased risk of hospital readmission among patients with oncological diseases may partly be related to their immunosuppressive treatments. Another study on patients in the United States revealed significantly higher rates of cancer among readmitted compared with non-readmitted patients [32]. According to the univariable analysis, the risk of readmission was also not different among patients suffering from chronic respiratory diseases and chronic renal diseases compared to those without, similarly to other studies [33]. However, these variables were left out from the multivariable analysis as they were not considered to add information to the model.

Patients with an initially short index hospital stay had a significantly higher risk of being readmitted [14, 22]. This seems to be a common observation once sufficient sample size is considered [34]. Others describe the disease course as a biphasic phenomenon starting with a mild clinical presentation, allowing for discharge, and later evolving into a worsened state [32]. Early discharge can also be frequent in moments of hospital saturation when resources are insufficient to handle the number of patients [14]. It is known that hasty discharges before the severity peak or complete recovery favour readmissions [35]. Readmissions could also relate to post-discharge care systems. In some health facilities, management of patients after discharge can be poorer than preventive hospital measures [14]. Although administrative prioritisations aim to reduce both length of stay and readmissions, these two goals seem inversely related [22].

Discharge to home at the end of the index hospitalisation was a risk for readmission compared to discharge to medical facilities (long-term care, rehabilitation, etc.), as opposed to other findings [9, 13, 36], all based in the United States, where readmission was less frequent among patients discharged to home. In the Netherlands [6], discharge to long-term care facilities increased the risk of hospital readmission. Reasons for such differences can reside in the low-level individual differences between hospitals' discharge decisions [37] or in the high-level differences between countries' medical care systems. In an analysis of the health systems for Switzerland and the Netherlands [38], Switzerland's system was described as more successful in its adaptation to changing societal constraints. Within Switzerland, quality of rehabilitation and intermediate-care facilities is ensured through an association, SwissREHA, accounting for more than 50% of all rehabilitation beds in the country [39]. As a possible proxy for COVID-19 rehabilitation, stroke rehabilitation was shown [40] to be conducted more efficiently in Switzerland than in the United States. Further studies accounting for insurance coverage of patients [14], governance and financing of healthcare systems and societal factors are necessary to learn more about this aspect.

Patients who were admitted to the IMCU or ICU during the index hospitalisation had a slightly lower risk of readmission, although the association was not statistically significant. Several other studies also found no significant association [14]. The first justification resides in a statistical bias. Due to a higher in-hospital death rate for those patients admitted to IMCU/ICU (20.2% compared to 9.1% for patients not admitted to IMCU/ICU), the readmission population is biased towards having fewer IMCU/ICU-admitted patients because a substantial proportion of them have already died during the index hospitalisation. The second explanation is that ICU admission is related to illness severity and cautions practitioners against a preemptive discharge [22]. In our data, more than 80% of patients who did not

spend time in the IMCU/ICU during the index hospitalisation were discharged to home, whereas it reduced to about 40% for patients who were admitted to the IMCU/ICU.

This study investigated the effect of the immunisation status on readmission odds and concluded that there was no significant effect. From a data perspective, the proportion of patients with unknown outcome for their index hospitalisation was 6.0% overall, but the missing data rose to 10.5% when focusing on patients fully immunised. The dataset was biased towards reflecting the outcomes of patients not or partially immunised, possibly because incomplete immunisation is viewed by the practitioners as a risk factor for COVID-19 severity or recurrence. High-risk, unvaccinated patients were more likely to die in hospital and therefore would be excluded from readmission analysis, while high-risk, vaccinated individuals were more likely to survive and contribute to the analysis [43]. It is important to take into consideration the specific vaccination context of Switzerland over the year 2021. In the first six months of 2021, people at high risk of severe COVID-19 (elderly, vulnerable and immunosuppressed individuals) were vaccinated in priority: a non-negligible part of them were less prone to respond to the vaccine. Then it became clear during the last six months of the year that elderly people who did not get their booster doses were also at greater risk of severe disease caused by the Delta variant (the Delta variant became dominant in Switzerland in July 2021). Considering the previously demonstrated vaccine efficacy and the described vaccination strategy in Switzerland during the study period, the study tends to report risk factors for readmission for lower-risk unvaccinated patients and higher-risk vaccinated patients.

Limitations

The limitations of this analysis resided in its observational nature and its imputed data. The reason for readmission was not recorded in our database, limiting the understanding of risk factors. Data on competing events such as death after discharge was not available for most patients: therefore, we were unable to perform a time-to-event analysis, and the probability of rehospitalisation may be slightly biased. The study may in general be subject to some selection bias: for example, certain patients such as those admitted to the ICU or IMCU, and those without proper immunisation, were at higher risk of death and thus exclusion, which may impact the association of these variables with rehospitalisation. There may also be differences in patient characteristics between the centres that the analysis did not control for. The definitions of some variables were not optimal, for example immunocompromised patients also include HIV-infected individuals under successful antiretroviral therapy. We had to restrict the study period to one year given that the collection and definition of variables evolved substantially over time. Therefore we were not able to include the early stages of the pandemic, nor the later waves dominated by the Omicron variant. Age was identified as having strong collinearity with many other risk factors; however the analysis removing the age variable did not change the significance of the risk factors presented above (see Appendix A.3).

Conclusion

We showed that older age, male sex, immunosuppression, discharge to home instead of a facility and oncological pathology were the main risk factors for hospital readmission identified within the CH-SUR Swiss-based surveillance system. Our findings can support the development and implementation of efficient patient management strategies for discharge, as well as support services and coordinated care networks such as post-discharge telehealth monitoring, to mitigate the risk of readmission. Moreover, further studies including immunisation status for the high-risk groups and other socioeconomic factors of patients could bring further elements to fully understand the hospital readmission dynamics among COVID-19 patients.

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Potential competing interests

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

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Appendix

A.1 Definitions

Immune status

- Fully immunized: patients with a base immunization and those with a booster. Patients with a base immunization are those who received one dose of the Johnson & Johnson (Janssen®) vaccine or two doses of the Moderna (Spikevax®), Pfizer/BioNTech (Comirnaty®), AstraZeneca (Vaxzevria®), Sinopharm®, Sinovac (CoronaVac®) or COVAXIN® vaccines (FOPH/Federal Vaccination Commission vaccination recommendation), and those with a documented prior infection or positive test (requiring hospitalization or not) who received one vaccine dose of the vaccines listed before, independent of the time between disease recovery and date of vaccination. Patients with booster are those with base immunization who received one or more additional vaccine doses (booster) with a minimum 4 months since the last vaccine application for the base immunization.
- Partially immunized: partially immunized patients (Patients who received one dose of the vaccines from Moderna (Spikevax®), Pfizer/BioNTech (Comirnaty®), AstraZeneca (Vaxzevria®), Sinopharm®, Sinovac (CoronaVac®) or COVAXIN® before the positive test and have no proof of previous SARS-CoV-2 infection), and those recovered from a previous SARS-CoV-2 infection (with confirmed previous SARS-CoV-2 infection, which required or not hospitalization in the past and are not vaccinated with any dose; independent of the time since previous infection).
- Not immunized: patients who had not received a single dose of any vaccine by the time of the positive SARS-CoV-2 test and had no proof of previous infection with this virus before the considered hospitalization.

Deconditioning syndrome

Deconditioning syndrome corresponds to the presence of a physical diminishment, weakening of the patient, or if his/her convalescence will take a lot of time.

Immunosuppression

Patients are considered as immunocompromised if they have a hematological pathology with immunosuppression, rheumatological or auto-immune pathology with immunosuppression, are receiving immunosuppressive treatment, or are HIV-positive.

Treatments

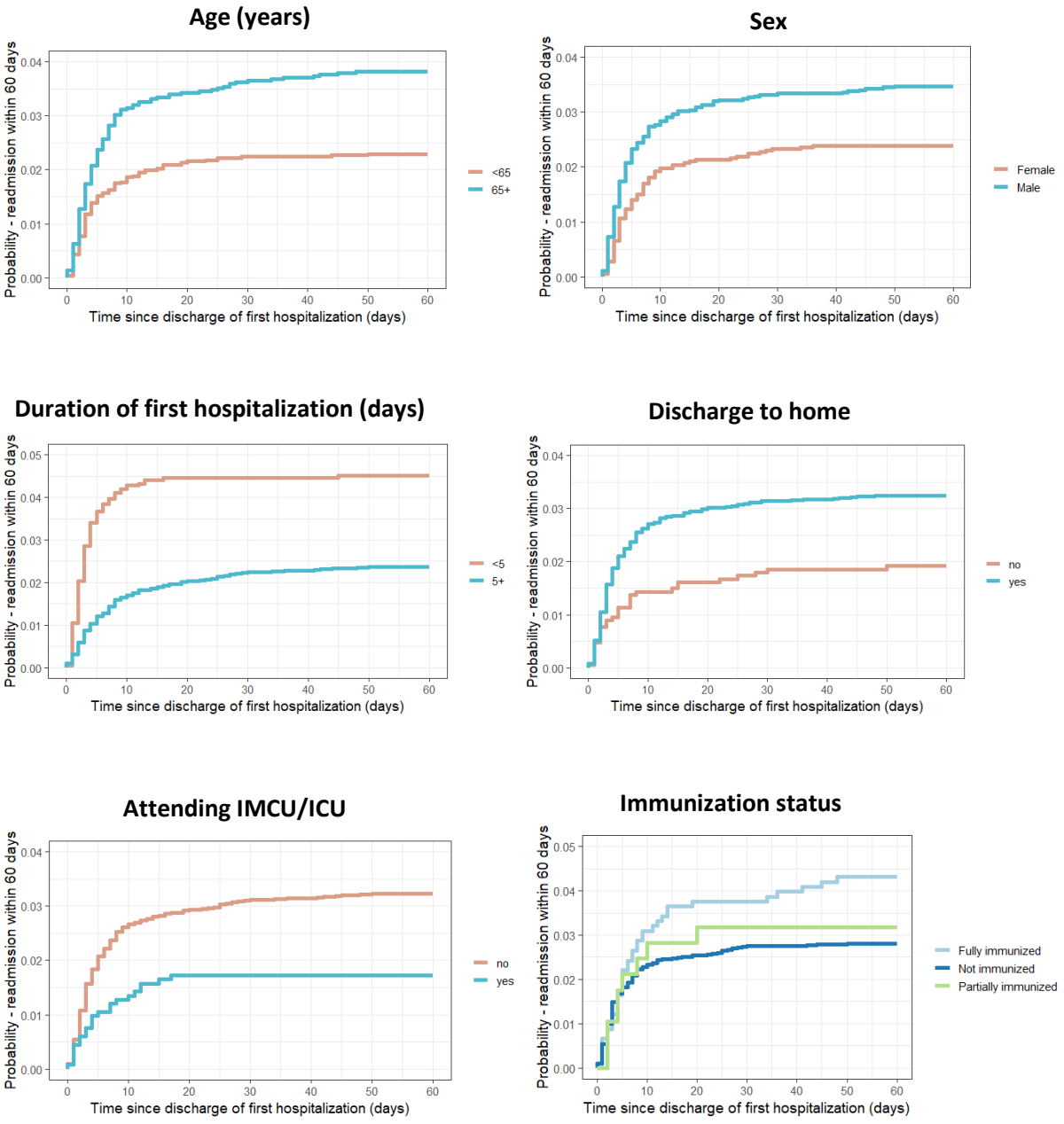
Patients are considered as having received a treatment during the course of their index hospitalization if they received any antiviral treatment (whether prophylactic or to treat SARS-CoV-2 infection), any antibody treatment against COVID-19, or any corticosteroid treatment against COVID-19.

Oncological pathology

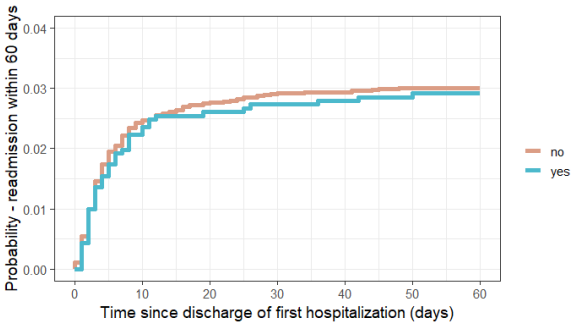
Oncological pathologies include for example cancer, tumors, etc., provided the person is currently suffering from it or suffered from it within the past 5 years.

A.2 Stratified cumulative incidence functions

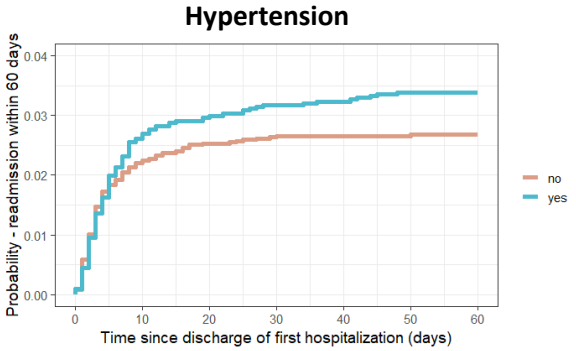
Cumulative incidence functions of readmission within 60 days, stratified per: age, sex, duration of index hospitalization, discharge at home for index hospitalization, any IMCU/ICU stay during index hospitalization, COVID-19 immune status (at index hospitalization), diabetes, hypertension, cardiovascular disease, renal disease, oncological pathology, obesity, respiratory disease, immunosuppression, any treatment during index hospitalization (at index hospitalization).



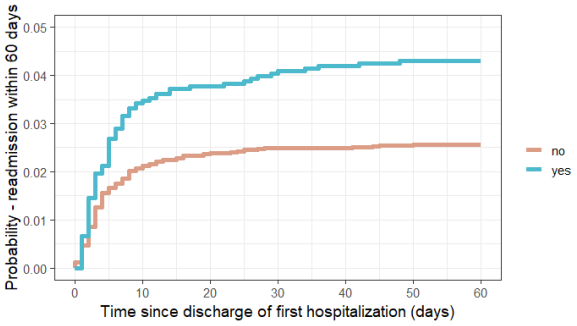
Diabetes



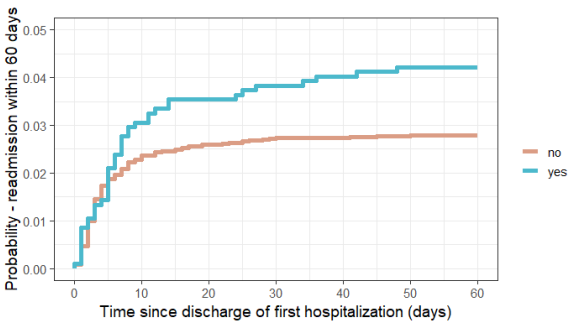
Hypertension



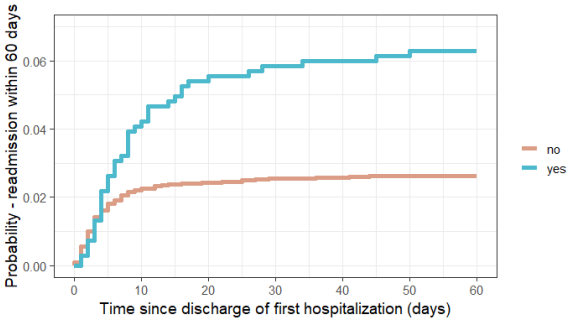
Cardiovascular disease



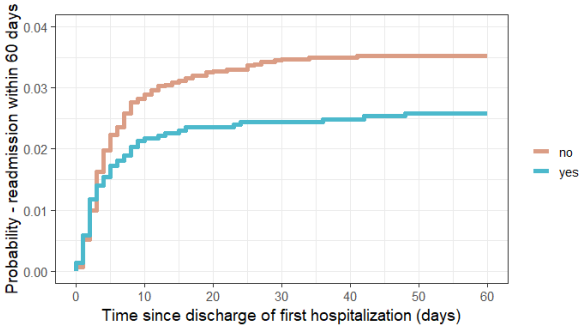
Renal disease



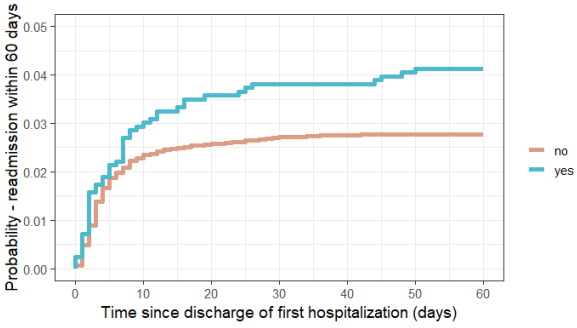
Oncological pathology



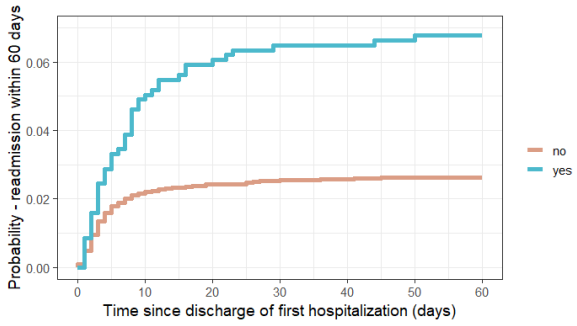
Obesity



Respiratory disease



Immunosuppression including HIV



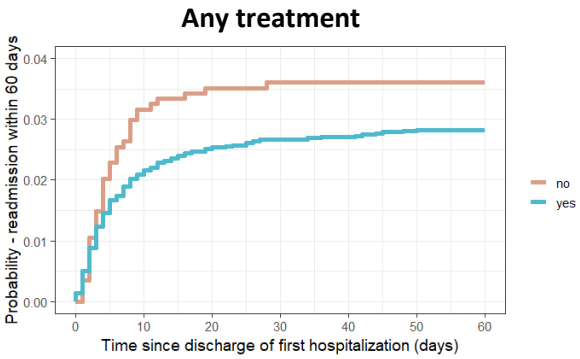


Figure. Cumulative incidence of readmission since discharge of first hospitalization stratified by different variables. See Appendix A.1 for full definitions of the variables.

A.3 Investigation of collinearity in the multivariable logistic regression model

We investigated the possible issue of collinearity between variables in the multivariable logistic regression model on complete cases, via pairwise Chi-squared tests between explanatory variables. The results are shown in the Figure below. Some significant collinearity between variables was found, particularly between age and all other covariables except sex.

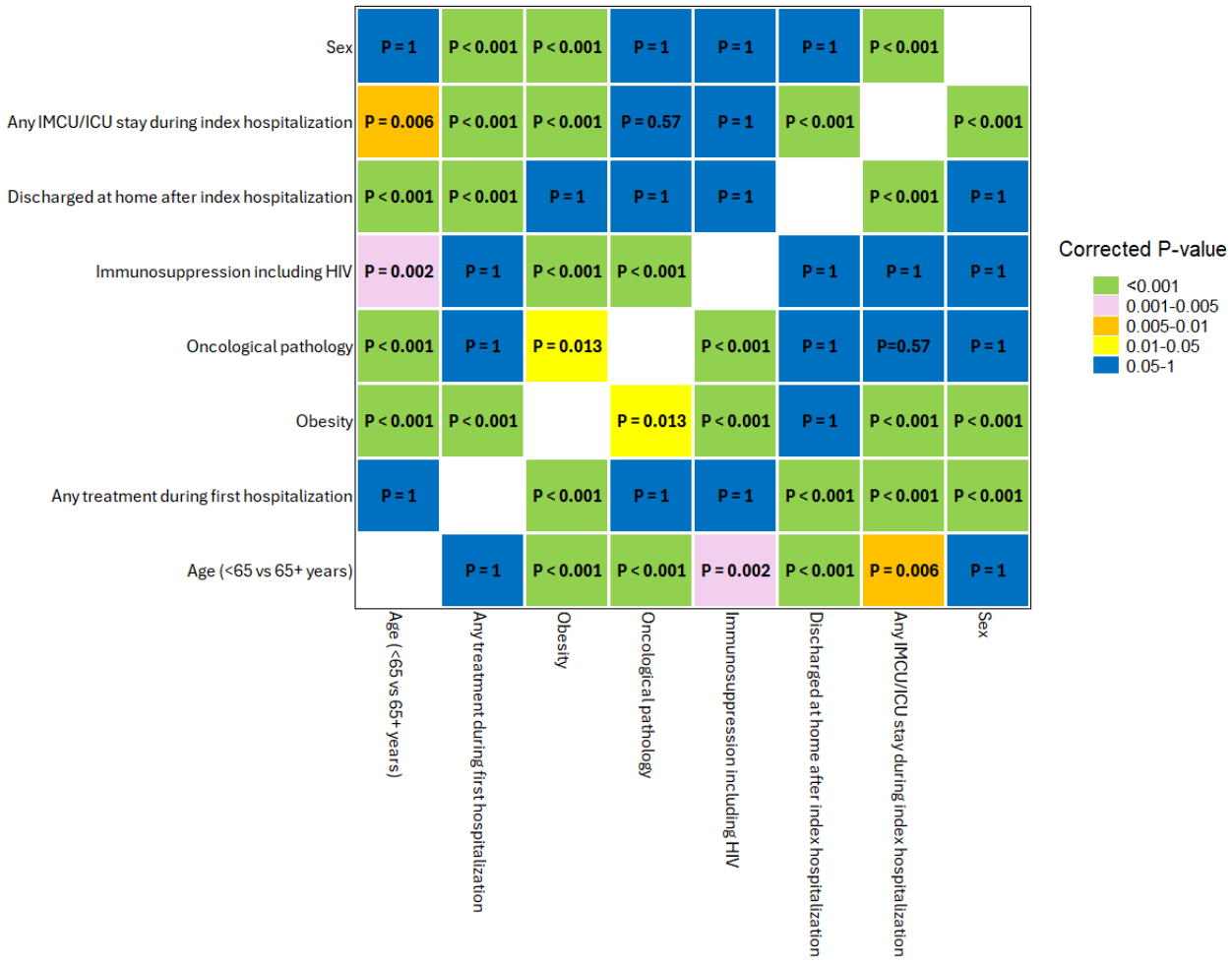


Figure. Corrected P-values from pairwise Chi-squared tests between explanatory variables of the multivariable logistic regression (complete cases).

Such patterns were expected: it is well known that some of the comorbidities among the explanatory variables are more common among older persons.

To evaluate the robustness of our logistic regression model given those collinearity patterns, we repeated our multivariable logistic regression fit removing one of the explanatory variables with the highest collinearity with the others, namely the age. Associated ORs can be found in Table A3.1 below. As can be seen, results are not essentially different from the reference analysis (Table 4 of the main manuscript). We also performed stratified analysis for individuals aged below and above 65 years, respectively. The direction of the associations remained the same as in the analysis of the full dataset. However, discharge to home was no longer significantly associated with rehospitalization in the younger age group, and the OR was also close to 1. In the older age group, immunosuppression lost is significance, although the odds for rehospitalization were still slightly higher than in patients not immunosuppressed.

Table A3.1: Odds ratios with 95% CI from multivariable logistic regression on complete cases (cc), without age as explanatory variable

	Multivariable (cc)	
Variable	Odds ratio (95% CI)	P-value
Sex		
Male	1 (ref)	0.06
Female	0.75 (0.53-1.03)	
Discharged at home for index hospitalization		
No	1 (ref)	0.02
Yes	1.50 (0.98-2.40)	
Any IMCU/ICU stay during index hospitalization		
	1 (ref)	
No		0.08
Yes	0.71 (0.42-1.12)	
Oncological pathology		
	1 (ref)	
no		<0.00001
yes	2.38 (1.56-3.54)	
Obesity		
	1 (ref)	
no		0.02
yes	0.70 (0.48-1.00)	
Immunosuppression		
no	1 (ref)	<0.001
yes	2.11 (1.38-3.15)	
Any treatment (at index hospitalization)		
no	1 (ref)	0.35
yes	0.83 (0.56-1.24)	

Table A3.2. Stratified analysis according to age (<65 years vs ≥65 years; multivariable, complete cases).

	Age <65 years		Age 65 years and above	
Variable	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Sex				
Male	1 (ref)	0.07	1 (ref)	0.33
Female	0.59 (0.35-0.99)		0.86 (0.56-1.32)	
Discharged at home for index hospitalization				
No	1 (ref)	0.58	1 (ref)	<0.001
Yes	1.08 (0.52-2.49)		2.14 (1.26-3.86)	
Any IMCU/ICU stay during index hospitalization				
	1 (ref)		1 (ref)	0.17
No		0.08		
Yes	0.73 (0.34-1.43)		0.71 (0.36-1.34)	
Oncological pathology				
	1 (ref)		1 (ref)	0.006
no		<0.001		
yes	2.73 (1.22-5.57)		1.93 (1.16-3.11)	
Obesity				
	1 (ref)		1 (ref)	0.25
no		0.08		
yes	0.71 (0.40-1.21)		0.77 (0.46-1.25)	
Immunosuppression				
no	1 (ref)	<0.0001	1 (ref)	0.42
yes	3.75 (2.01-6.69)		1.28 (0.69-2.23)	
Any treatment (at index hospitalization)				
no	1 (ref)	0.58	1(ref)	0.44
yes	0.84 (0.46-1.61)		0.81 (0.49-1.40)	