Outcomes of Hospital-Acquired COVID-19 in the Canadian First Wave Epicenter: A Retrospective Study

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Abstract

Background: The outcome of hospital-acquired (HA) coronavirus disease 2019 (COVID-19) remains uncertain. Mortality data from published small cohorts are contradictory. We aimed to assess whether mortality is higher in HA cases than in non-hospital-acquired (NHA) cases and determine the prevalence of HA-COVID-19 in our hospital.

Methods: This retrospective single-centre cohort study included all COVID-19 positive adults admitted to Hôpital Maisonneuve-Rosemont (Montreal, Canada) from March 1st to June 30th, 2020. Data on demographic characteristics, comorbidities, treatment, ICU admission and mechanical ventilation (MV) requirements were collected from electronic health records. Hospital acquisition was adjudicated based on the timing of symptom onset, SARS-CoV-2 PCR testing and exposures. To evaluate the association between HA-COVID-19 and in-hospital mortality, we computed a multivariate logistic regression analysis including known risk factors for death in COVID-19 patients as co-variates.

Results: Among 697 COVID-19 patients, 254 (36%) were classified as HA. The mortality rate was higher in HA group compared to NHA group (38.2% vs. 26.4%, p=0.001), while the rates of ICU admission (8.3% vs. 19.2%, p=0.001) and MV requirement (3.5% vs. 13.0%, p=0.001) were lower. Multivariable logistic regression analysis demonstrated that HA-COVID-19 in patients under 75 is an independent risk factor for death (OR, 2.69; 95% CI 1.39-5.19, p=0.003).

Interpretation: To our knowledge, this is the largest single-centre cohort of HA-COVID-19 cases. These results show that HA-COVID-19 in younger patients was associated with higher mortality. Even in the face of pandemic fatigue, these findings justify taking

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extraordinary measures to prevent COVID-19 hospital transmission and avoid preventable death.

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INTRODUCTION

As of February 2021 in Canada, approximately 850,000 cases have been confirmed since the beginning of the pandemic, with over 21,700 deaths(1). During the first wave of this pandemic, the province of Quebec had the highest number of SARS-CoV-2 infections and Montreal was the epicenter, accounting for over a third of all infections in the province(2). In general, approximately 10% of COVID-19 patients require hospitalization and between 3–5% require intensive care unit (ICU) admission(3, 4). Older patients and those with existing comorbidities are at higher risk of adverse outcomes(4). Amidst this pandemic, hospitals must continue their usual activities and provide urgent care. Unfortunately, they are also a potential environment for viral transmission to vulnerable patients(5). As of February 2021, there has been sparse and contradictory data about hospital-acquired (HA) COVID-19 patient outcomes compared to non-hospital-acquired (NHA) COVID-19 patients as well as in-hospital transmission dynamics. Some studies showed a case fatality rate as high as 36% for HA-COVID-19 patients(6), while others reported a mortality rate lower than NHA-COVID-19 cases(7). Therefore, we aimed to assess whether mortality and complications were increased in HA cases when compared to NHA cases. We also explored the role of patients sharing multi-bedded rooms on COVID-19 in-hospital transmission.

METHODS

Study design and setting

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We conducted a retrospective cohort study through chart review at Hôpital Maisonneuve-Rosemont, a tertiary academic hospital built in 1954 and hosting 544 beds, including 16 ICU beds in Montreal, Quebec, Canada. On March 20th, 2020, it was designated as a COVID-19 care centre by the Quebec Ministry of Health and Social Services, hence receiving transfers from other institutions. Before this date, most COVID-19 patients presenting to our centre were transferred to other hospitals. During the first wave of the pandemic, up to 191 designated beds for confirmed COVID-19 were made available in our centre, including 19 ICU COVID-19 beds. The Research Ethics Board of the CIUSSS de l'Est-de-l'Île-de-Montréal approved our study protocol. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines(8).

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Participants

All COVID-19 patients aged 18 years or older hospitalized in our institution from March 1st to June 30th, 2020, were included in our analysis. COVID-19 infections occurring more than two weeks before hospitalization were excluded (Figure 1). The list of all COVID-19 patients was provided by the Infection Prevention and Control (IPAC) division, which prospectively tracked all COVID-19 positive patients in our institution. This list was then linked and cross-matched with our hospital administrative dataset to determine which patients were hospitalized.

Data sources/measurement

Members of the research team manually extracted the information from electronic health records. Study data were collected and managed using REDCap (Research Electronic Data Capture)(9). We gathered data on demographic characteristics, place of origin before hospitalization, deprivation index based on postal code(10), comorbidities based on the Charlson Comorbidity Index score (CCI), treatment, as well as the need for mechanical ventilation (MV) and ICU admission(11).

Case definitions

COVID-19 was defined as at least one positive SARS-CoV-2 PCR test (combined throat and nasopharyngeal swab or lower respiratory tract aspiration). We used the date of the first positive test if multiple tests were performed. We then classified cases as HA or NHA using definitions from the *Institut National de Santé Publique du Québec* (INSPQ)(12). Proven HA infections were defined as a positive COVID-19 test >14 days after hospital admission or when an in-hospital epidemiological link was identified with a known COVID-19 positive person by the IPAC division. Suspected HA infections were defined as occurring 7 to 14 days after hospital admission. Community-acquired (CA) cases were defined as occurring <7 days after hospital admission. The Medical Director of IPAC, unaware of each patient's outcome, reviewed all uncertain cases. For our analysis, we combined proven and suspected HA cases as HA infections to match other published studies(6, 13). CA cases and infections acquired in long-term care facilities or any other congregate living settings were classified as NHA cases.

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Infection Prevention and Control (IPAC) and testing practices

IPAC and testing practices changed during the pandemic's first wave, reflecting evolving knowledge and scaling up of SARS-CoV-2 PCR testing availability (Supplement eTable1). Visitor restrictions were rapidly implemented. COVID-19 patients were hospitalized on designated COVID-19 wards. Droplet and contact precautions were required when caring for suspected or confirmed COVID-19 patients, with personal protective equipment (PPE) including procedure mask, eye protection, isolation gown and gloves. N95 respirators were reserved for aerosol-generating medical procedures or patients presenting with predefined severity criteria concordant with INSPQ guidelines. However, our hospital was affected by PPE and hand sanitizer shortages, leading to a suboptimal uptake of some IPAC practices. Symptomatic healthcare workers and those with significant exposure to a known COVID-19 positive person were asked to stay home, received testing, and were managed by Occupational Health and Safety Division. All COVID-19 naive patients with significant exposure to a COVID-19 carrier were prospectively flagged by IPAC as close contacts and followed a 14-day quarantine under droplet and contact precautions, with daily symptom monitoring, and eventually repeated PCR testing. When COVID-19 outbreaks occurred on wards, the following additional measures were put in place: high-touch surface disinfection, restricted patient transfers, implementation of droplet and contact precautions for all the patients, daily symptom monitoring and SARS-CoV-2 PCR testing if symptoms developed, and eventually repeated testing of all patients even if asymptomatic.

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Outcomes

The primary clinical outcome was in-hospital mortality. Secondary clinical outcomes were hospital length of stay (LOS), dispositions at discharge for survivors, and hospital readmission rates up to 90 days after discharge. Additionally, we looked at the prevalence of HA-COVID-19 patients and COVID-19 acquisition in close contact patients that shared a multi-bedded room with known COVID-19 patients during their period of contagiousness (from 2 days before symptom onset to 10 days after). COVID-19 acquisition was linked to transmission between patients in the same room only if close contacts developed symptoms (or tested positive if asymptomatic) ≥3 days after the index patient symptom onset and their first contact, and up to 14 days after their last contact.

Statistical methods

We presented continuous variables as mean or median with their central distribution and categorical variables as proportions. Outcome comparison between HA vs. NHA groups was performed using Chi-square test for categorical data and calculation of Mantel-Haenszel odds ratios. To evaluate the association between HA-COVID-19 and in-hospital mortality, we performed a multivariate logistic regression with an epidemiological model by including the following known risk factors for death in COVID patients as co-variates; age, sex, moderate to severe chronic renal disease, solid tumor, hematological malignancy, diabetes, chronic obstructive pulmonary disease (COPD) and myocardial infarction. Considering the potential interaction between age and hospital

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acquisition status on mortality and the presence of effect modification on univariate analysis, the impact measure of HA-COVID-19 was stratified by age in the multivariable analysis with a linear combination of coefficients using the lincom command in STATA. We tested for collinearity using Variance Inflation Factors (VIFs). As a sensitivity analysis, we performed the same analysis for only proven HA cases after excluding all suspected HA cases. All analysis was performed using STATA MP version 16.1.

RESULTS

Participants

After data linkage, 734 patients were screened for inclusion and 37 were excluded, resulting in 697 hospitalized COVID-19 patients (Figure 1). The first COVID-19 patient admitted to our hospital was on March 19th and the first HA case became symptomatic on March 24th. Subsequent cases are depicted on the epidemic curve (Figure 2). A total of 254 (36.4%) COVID-19 patients were classified as being HA [proven: 217 (85.4%); suspected: 37 (14.6%)]. Among HA-COVID-19 proven cases, 101 (46.5%) had a positive SARS-CoV-2 PCR test >14 days after admission; the 116 others had an epidemiological link identified. Out of 139 identified close contact patients associated with sharing a multi-bedded room with a COVID-19 case, 45 (32.4%) became COVID-19 positive during hospitalization, and six after discharge.

The median age was 75 years old [IQR 62-85] and 356 (51.1%) patients were female (See Table 1). Being under 75 years of age was less frequent in the HA group (N=100, 39.4%, p=0.007) than in the NHA group (N=229, 51.7%). HA-COVID-19 patients had a higher

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prior 5-year history of cancer (localized N=49, 19.3% vs. N=39, 8.8%; metastatic N=27, 10.6% vs. N=15, 3.4%; p=0.001) and COPD (N=59, 23.2% vs. N=66, 14.9%, p=0.006). Surgical procedures were performed more frequently in HA-COVID-19 patients compared to NHA-COVID-19 patients (N=37, 14.6% vs. N=13, 2.9%; p=0.001). Steroid treatment was prescribed in 46 (18.2%) HA patients and 66 (14.9%) NHA patients (p=0.27). Two patients received tocilizumab and three patients received hydroxychloroquine. Both treatments were not recommended for COVID-19 at the time of our study.

Clinical outcomes

As shown in Table 2, HA-COVID-19 patients had a higher rate of in-hospital mortality (N=97, 38.2%) compared to NHA-COVID-19 patients (N=117, 26.4%, p=0.001), with lower rates of ICU admission and MV requirement (N=21, 8.3% vs. N=85, 19.2%, p=0.001 and N=9, 3.5% vs. N=58, 13.0% respectively, p=0.001). Most ICU COVID-19 patients were admitted within 7 days of a positive test (N=17, 81.0% in HA group vs. N=74, 87.1% in NHA group, p=0.47). HA-COVID-19 survivors were discharged home significantly less and transferred more to rehabilitation centres compared to NHA-COVID-19 patients (p=0.001). Readmissions within 90 days after discharge occurred more frequently in the HA group than in the NHA group (N=24, 15.3% vs. N=13, 4.0%, p=0.001).

After multivariate analysis, patients under 75 years of age with HA-COVID-19 had significantly increased odds of death than hospitalized NHA-COVID-19 patients (OR, 2.69; 95% CI, 1.39 to 5.19; p=0.003) (Table 3). There was no increased risk of death for

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older patients (OR, 1.15; 95% CI 0.59 to 2.22; p=0.687 in the 75-84 age group and OR, 0.73; 95% CI 0.40 to 1.32; p=0.30 in the ≥85 age group). Moderate to severe chronic renal disease, solid metastatic cancer, and hematological malignancy were all associated with an increased odds of death in our cohort. Conversely, being female seemed protective (OR, 0.61; 95% CI 0.42 to 0.87; p=0.007). In the sensitivity analysis after excluding suspected HA cases, HA COVID-19 status remained a significant risk factor for mortality (Supplementary Material eTable 1). No significant collinearity was detected between our co-variates.

INTERPRETATION

In the present study, one-third of all hospitalized COVID-19 cases were acquired due to in-hospital transmission, with a significant increase in mortality rates.

Similar data from England reported that approximately 25% of hospitalized COVID cases were acquired during hospital stay(14). A major factor influencing the prevalence of HA-COVID-19 infection is the hospital's infrastructure. Most of our wards had no mechanical ventilation systems and had two-bedded and even four-bedded rooms with patients separated by curtains. This design might explain why one-third of patients sharing a room with a COVID-19 patient subsequently developed COVID-19. This proportion is consistent with household transmission rates between spouses (37.8%, 95% CI 25.8%-50.5%) reported in a recent meta-analysis(15). While only 45/254 (17.7%) HA-COVID-19 cases were directly linked to transmission between patients in a multi-bedded room, more HA cases might be indirectly linked to high population density(6). The importance

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of crowding on COVID-19 incidence and mortality has already been demonstrated in Canadian long-term care settings(16). While difficult to quantify, various shortages (e.g., medical mask, PPE, hand sanitizer) might have also impacted transmission rates(17, 18). Nonetheless, as shown by Brigham and Women's hospital's first wave experience in Boston, Massachusetts, under optimal conditions in-hospital transmission can be limited: of the 697 COVID-19 hospitalizations, only 1 case was deemed to be HA-COVID-19(19). With new variants being of concern for increased transmissibility and potentially associated with an increased risk of death, it is even more important to reinforce nonpharmaceutical interventions to prevent nosocomial SARS-CoV-2 transmission (20, 21).

The mortality rate of HA-COVID-19 patients in our study is also similar to existing data in the literature(3, 6). Our NHA-COVID-19 group provided a good representation of the most severe CA-COVID-19 patients, with 91.2% of the total NHA cases being community-acquired and a mortality rate of 26.4%. Nonetheless, HA-COVID-19 patients still had a higher mortality rate. A cohort study of 252 hospitalized patients with COVID-19 and active cancer, HA-COVID-19 was an independent risk factor of mortality (HR, 2.3; 95% CI 1.3 to 4; p=0.005). Their mortality rate in the HA-COVID-19 group was higher than our results (47% vs. 38%), likely due to their cohort being exclusively cancer patients(22). Similarly, a history of metastatic cancer and hematological malignancies were independent risk factors for death in our study. In another cohort study, HA-COVID-19 was not a risk factor for death compared to NHA-COVID-19 (HR, 0.71; 95% CI, 0.51 to 0.98)(7). However, they did not stratify for age. The estimated risk of death for COVID-

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19 infection in hospitalized octogenarians is 60% irrespective of modes of acquisition(23). Therefore, the added physiological stress of COVID-19 on a hospitalized patient already weakened by an acute illness is probably irrelevant for those with severe underlying frailty and comorbidities. Interestingly, the increased risk of death from the in-hospital acquisition of COVID-19 was only significant in younger patients in our analyses. Also, subsequent SARS-CoV-2 infection in hospitalized patients led to potentially sicker patients or may be perceived this way by their treating physicians. This possibly could have led patients and physicians into taking a more conservative approach, reflected by overall fewer ICU admissions and use of MV. It is difficult to compare the intensity of care in the two groups since their levels of care were often discussed and changed once the disease was well advanced.

To our knowledge, this study is the largest published cohort of HA-COVID-19 cases. We used clear criteria to determine the type of acquisition and all uncertain attribution were reviewed by the Medical Director of IPAC for adjudication.

Limitations

There are limitations to our study. First, it is a single-centre study, therefore limiting the generalizability of our in-hospital COVID-19 transmission data. Second, SARS-CoV-2 PCR testing capacity and indications changed quickly at the beginning of the pandemic, potentially underestimating the prevalence of asymptomatic and pauci-symptomatic HA-COVID-19 in the first weeks. Third, there was no systematic post-discharge follow-up to assess if patients developed COVID-19 following potential in-hospital exposure,

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possibly underestimating HA-cases and COVID-19 acquisition by close contacts. Fourth, some multi-bedded room close contact patients could have developed COVID-19 from the same exposure as the index case in their room (e.g., an asymptomatic COVID-19 positive healthcare worker). This was mitigated by excluding secondary cases with a serial interval smaller than 3 days.

Conclusion

For patients under the age of 75, hospital acquisition of COVID-19 infections resulted in a higher risk of death than community COVID-19 cases requiring hospitalization. Like residents in long-term care facilities, hospitalized patients are vulnerable and at increased risk of complications if exposed to SARS-CoV-2. In-hospital viral transmission remains a major concern for patients as many hospital design features are challenging to correct and circulating variants of COVID-19 now seem more contagious. More so, some have a realistic probability of being associated with an increased risk of death. Even in the face of pandemic fatigue, these findings justify taking extraordinary measures to prevent COVID-19 hospital transmission and avoid preventable death.

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Table 1. Baseline characteristics between hospital-acquired and non-hospital-acquired COVID-19 patients.

Characteristics	Hospital-acquired N= 254 (36.4%)	Non-hospital-acquired N= 443 (63.6%)	P value
Age, median [IQR]	79 [68-86]	74 [59-85]	
Age (years), n (%)			0.007
<75	100 (39.4)	229 (51.7)	
75-84	71 (27.9)	100 (22.6)	
≥ 85	83 (32.7)	114 (25.7)	
Female sex, n (%)	128 (50.4)	228 (51.5)	0.79
Comorbidities, n (%)*			
Moderate to severe chronic kidney disease**	34 (13.4)	53 (12.0)	0.59
Solid tumor			0.001
Localized	49 (19.3)	39 (8.8)	
Metastatic	27 (10.6)	15 (3.4)	
Hematological malignancy	12 (4.7)	10 (2.3)	0.073
Diabetes	86 (33.9)	157 (35.4)	0.67
COPD	59 (23.2)	66 (14.9)	0.006
Myocardial infarction	19 (7.5)	32 (7.2)	0.90
Dementia	57 (22.4)	102 (23.0)	0.86
Charlson comorbidity Index, median [IQR]	2 [1-4]	2 [0-3]	
Provenance before admission, n (%)#			<0.001
Home	181 (71.3)	236 (53.3)	
Long-term care facility	9 (3.5)	49 (11.1)	
Others	64 (25.2)	158 (35.7)	
Depreviation index of 4 or 5, n (%)***	152 (59.8)	241 (54.4)	0.19
Steroids treatment, n (%)	46 (18.1)	66 (14.9)	0.27
Surgical procedure, n (%)	37 (14.6)	13 (2.9)	0.001
ICU admission, n (%)	21 (8.3)	85 (19.2)	0.001
ICU admission within 7 days, n (%)	17 (81.0)	74 (87.1)	0.47
Mechanical ventilation, n (%)	9 (3.5)	58 (13.1)	0.001

* Selected comorbidities from the Charlson Comorbidity Index

** Moderate to severe chronic renal disease defined as creatinine > 265 umol/L

Provenance before admission, others: congregate living settings such as RPA (Private Elderly Residence), IR-FTR (Intermediate and Family-Type Resources), transfer from another hospital and rehabilitation.

*** The deprivation index is based on patient postal code and 2016 census data. Results of various indicators are aggregated to create a deprivation index to identify underprivileged population. A score from 1 (highly privileged) to 5 (highly underprivileged) is calculated, with 4 and 5 signifying being underprivileged and highly inderpriviledged.

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IQR: interquartile range, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit

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Table 2. Outcomes in patient with hospital-acquired and non-hospital-acquired COVID-19 infection.

COVID-19 outcomes	Hospital-acquired N=254 (36.4 %)	Non-hospital-acquired N= 443 (63.6%)	P value
Mortality, n (%)*	97 (38.2)	117 (26.4)	0.001
<75 years old	29 (29.0)	23 (10.0)	
75-84 years old	32 (45.1)	38 (38.0)	
≥85 years old	36 (43.4)	56 (49.1)	
Hospital length of stay, median [IQR]	24.5 [9-40]	8 [2-15]	
Disposition at discharge, n (%)**			0.001
Home	76 (48.4)	195 (59.8)	
Long-term care facility	32 (20.4)	73 (22.4)	
Rehabilitation	27 (17.2)	19 (5.8)	
Others***	22 (14.0)	39 (12.0)	
Readmission within 90 days after discharge, n (%)	24 (15.3)	13 (4.0)	0.001

* Mortality stratified by age

** Disposition at discharge were only calculated for survivors (N=157 in HA group and N=326 in NHA group)

*** Others: congregate living settings such as RPA (Private Elderly Residence), IR-FTR (Intermediate and Family-Type Resources) and transfer to another hospital or dedicated centres for quarantine of COVID-19 cases.

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Table 3. Multivariate logistic regression of factors associated with COVID-19 mortality

Factors	Odds Ratio	95 % Confidence interval	P value
Hospital-acquired COVID-19*			
<75 years old	2.69	1.39 to 5.19	0.003
75-84 years old	1.15	0.59 to 2.22	0.69
≥85 years old	0.73	0.40 to 1.32	0.30
Sex			
Female	0.61	0.42 to 0.87	0.007
Solid tumor			
Localized	1.08	0.64 to 1.83	0.77
Metastatic	6.02	2.90 to 12.52	0.001
Hematological malignancy	6.77	2.45 to 18.7	0.001
Moderate to severe chronic renal disease**	2.97	1.74 to 5.04	0.001
Diabetes	1.20	0.81 to 1.77	0.36
COPD	1.03	0.65 to 1.63	0.90
Myocardial infarction	0.90	0.47 to 1.73	0.75

* In-hospital acquisition of COVID-19 Odds Ratios was stratified by age

** Moderate to severe chronic renal disease defined as creatinine > 265 umol/L COPD: COPD: chronic obstructive pulmonary disease

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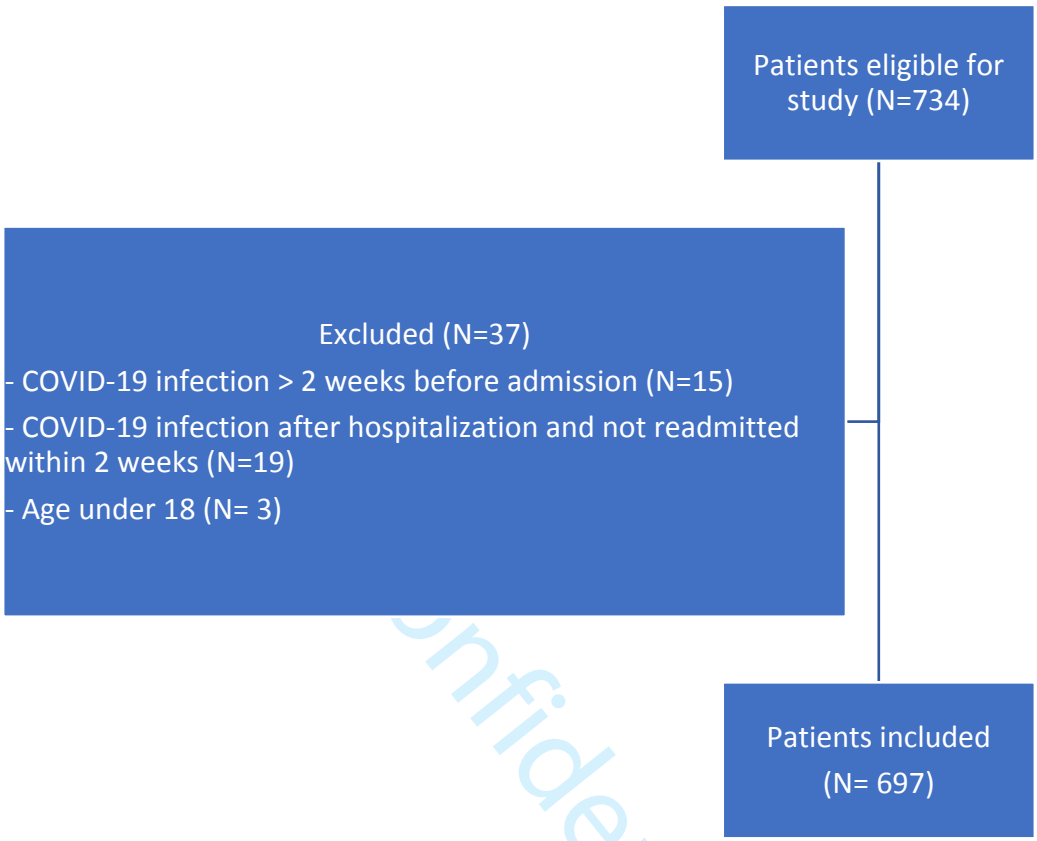
Figure 1. Flow chart of COVID-19 admitted patients included in our study



Flow chart detailing the inclusion and exclusion of patients in our cohort, resulting in a total of 697 hospitalized COVID-19 patients.

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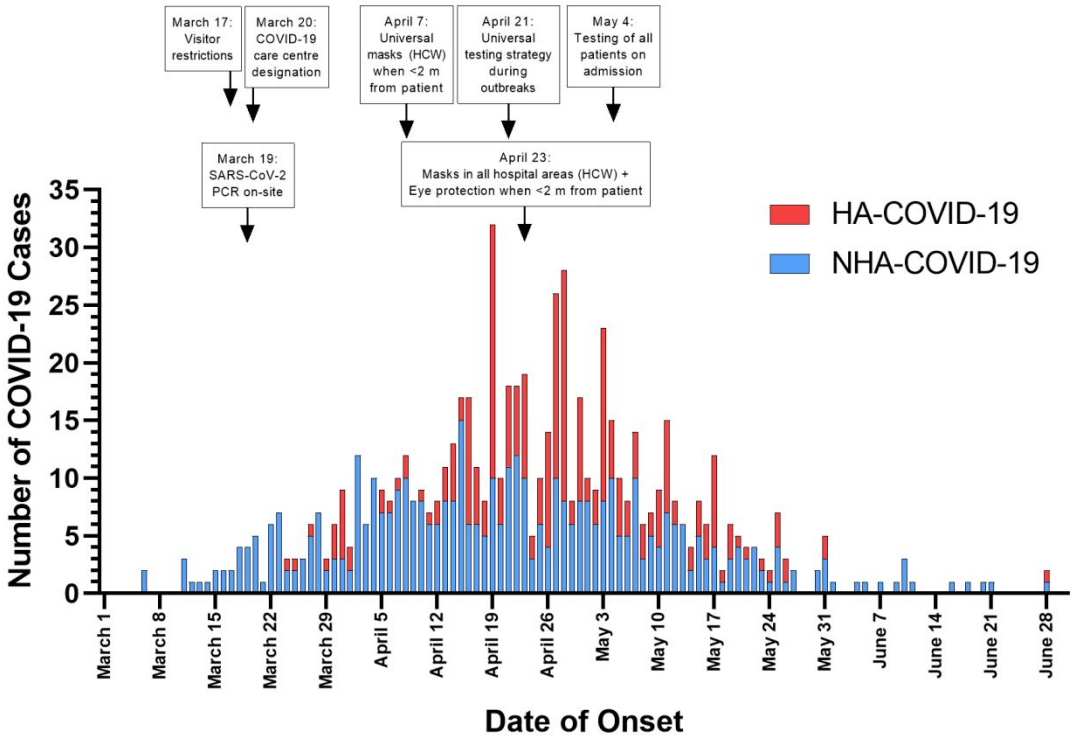
Figure 2. Epidemic curve of hospitalized COVID-19 patients



Epidemic curve demonstrating the occurrence of COVID-19 in our institution for both HA (in red) and NHA-COVID-19 cases (in blue). Date of onset reflects the symptom onset. If the patient remained asymptomatic, the date reflects the first positive SARS-CoV-2 PCR test.

HCW: Healthcare worker

For Peer Review Only

Supplementary Material

eTable 1. Timeline of selected important events during the first wave

Date	Events
March 17th	Visitor restrictions
March 19th	SARS-CoV-2 PCR implemented on-site at the hospital laboratory
March 20th	COVID-19 care centre designation for the hospital and opening of the first COVID-19 ward
March 26th	Stopped sending samples to public health reference laboratory for SARS-CoV-2 PCR confirmation
March 30th	First COVID-19 outbreak on a ward. Implementation of a universal masking policy on outbreak ward in response.
April 4th	Opening of 2nd COVID-19 ward
April 7th	Universal masking policy implemented for all healthcare workers within 2 meters of patients
April 8th	Opening of 3rd COVID-19 ward
April 10th	Directive about prolonged use of medical mask
April 16th	Outbreak on a 2nd ward
April 17th	Outbreak on a 3rd and 4th ward
April 17th	Opening of 4th COVID-19 ward
April 21st	Outbreak on a 5th ward
April 21st	Introduction of a universal testing strategy for all patients on wards in outbreak (testing symptomatic and asymptomatic alike)
April 23rd	Outbreak on a 6th ward
April 23rd	Universal masking policy extended to all hospital areas, not just within 2 meters of patients Universal eye protection policy implemented for all healthcare workers within 2 meters of patients
May 4th	SARS-CoV-2 PCR testing for all patients on admission
May 25th	Outbreak on a 7th ward
May 18th – June 10th	Progressive end of all the outbreaks on various wards
May 25th – June 5th	Closure of all COVID-19 wards except one

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eTable 1. Multivariate logistic regression of factors associated with COVID-19 mortality after excluding all suspected HA-COVID-19 cases.

Factors	Odds Ratio	95 % Confidence interval	P value
Hospital-acquired COVID-19*			
<75 years old	2.47	1.25 to 4.89	0.010
75-84 years old	1.00	0.49 to 2.04	0.99
≥85 years old	0.70	0.37 to 1.32	0.27
Sex			
Female	0.59	0.40 to 0.86	0.007
Solid tumor			
Localized	1.04	0.59 to 1.83	0.90
Metastatic	5.22	2.44 to 11.14	0.001
Hematological malignancy	7.11	2.56 to 19.76	0.001
Moderate to severe chronic renal disease**	3.12	1.79 to 5.41	0.001
Diabetes	1.22	0.81 to 1.83	0.34
COPD	0.92	0.57 to 1.50	0.74
Myocardial infarction	1.09	0.55 to 2.13	0.81

* In-hospital acquisition of COVID-19 was stratified for age
** Moderate to severe chronic renal disease defined as creatinine > 265 umol/L
COPD: chronic obstructive pulmonary disease

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