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Original Article

Impact of In-Hospital infection with SARS-CoV-2 among Inpatients at a university hospital

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A B S T R A C T

Objective: The objective of this study was to evaluate the incidence of nosocomial infection and the impact of cross-transmission of SARS-CoV-2 among inpatients at a tertiary care teaching hospital.
Methods: This was a retrospective cohort study involving inpatients admitted to a tertiary university hospital in the city of São Paulo, Brazil, between March 2020 and February 2021. Cases were identified on the basis of a positive reverse-transcription polymerase chain reaction result for SARS-CoV-2 and the review of electronic medical records. Nosocomial transmission was defined by applying the criteria established by the Brazilian National Health Regulatory Agency.
Results: We identified 2146 cases of SARS-CoV-2 infection, 185 (8.6%) of which were considered cases of nosocomial transmission. The mean age was 58.3 years. The incidence density was 1.78 cases per 1,000 patient-days on the general wards, being highest on the cardiac surgery ward, and only 0.16 per 1,000 patient-days on the COVID-19 wards. Of the 185 patients evaluated, 115 (62.2%) were men, 150 (81.1%) cases had at least one comorbidity, and 104 (56.2%) evolved to death.
Conclusions: Despite the preventive measures taken, nosocomial transmission of SARS-CoV-2 occurred throughout our hospital. Such measures should be intensified when the incidence of community transmission peaks.
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INTRODUCTION

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which can result in coronavirus disease 2019 (COVID-19), has caused an unprecedented global pandemic. Because COVID-19 is a highly contagious disease, there have been high numbers of hospital admissions, which has prompted health care facilities to adapt their capacity and infrastructure to implement the infection control measures needed in order to contain hospital outbreaks.[1]

As of February 27, 2021, there had been 113,784,735 confirmed cases of COVID-19 worldwide, and Brazil ranked third in the world, with 10,517,232 cases.[2] The colonization pressure resulting from the hospitalization of patients of COVID-19 creates a highly dangerous scenario, because it poses a risk to all of the professionals who work in the hospitals, as well as to family members and other hospitalized patients who have not been diagnosed with SARS-CoV-2 infection.[3]

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During the 2002 outbreak caused by SARS-CoV, 22% and 40% of the cases in China and Canada, respectively, occurred in health care workers (HCWs).[4] During the outbreak caused by the Middle East respiratory syndrome coronavirus in 2012, HCWs accounted for 42% of the cases reported in the United Arab Emirates city of Abu Dhabi.[5]

In-hospital transmission of SARS-CoV-2 is a problem that has been reported in several studies.[6-11] More than half of the patients analyzed in such studies have not presented with respiratory symptoms, and some have exhibited atypical clinical phenotypes during the incubation period,[8] thus raising major concerns for health care facilities. The SARS-CoV-2 pandemic has imposed a burden on hospitals, including numerous issues related to the specificities of the disease and the longer hospital stays, complicating in-hospital logistics and making it more difficult to manage the potential vectors of transmission.[12]

The objective of this study was to evaluate the incidence of nosocomial infection with SARS-CoV-2 and the impact of such infection among patients admitted to a tertiary care teaching hospital. We also attempt to identify higher risk situations in the various inpatient wards, providing epidemiological data to facilitate the implementation of measures for the prevention of nosocomial SARS-CoV-2 infection.

METHODS

Design and population

This was a retrospective cohort study involving patients admitted to the Hospital São Paulo—a tertiary care teaching hospital operated by the Federal University of São Paulo, in the city of São Paulo, Brazil—between March 2020 and February 2021. The hospital was built in 1960 and has a total of 750 beds, located either in two-bed rooms or on open wards.

During the first surge of the pandemic, the Hospital São Paulo became a referral center for COVID-19, 450 of its 750 beds being prioritized for patients with COVID-19. Infection control measures specifically directed toward prevention of SARS-CoV-2 transmission were implemented in accordance with the guidelines established by the US Centers for Disease Control and Prevention, the World Health Organization, and the Brazilian National Ministry of Health. In addition to the hospital infection control team, a special committee in the hospital was convened in order to ensure that the new measures were implemented properly. Elective surgical procedures were temporarily suspended. Visitation was banned in order to control the flow of people into the wards. Although one of the new measures were training staff in how to handle patients with COVID-19 and HCWs cohort, these measures were not always implemented, because there was a shortage of HCWs. In the emergency room, three patients' cohorts were established for outpatients and walk-ins: SARS-CoV-2-negative cases; suspected cases of COVID-19; and confirmed cases of COVID-19. Because there was also a shortage of reverse transcription-polymerase chain reaction (RT-PCR) tests, patients who had no symptoms of COVID-19 or history of contact with a case of COVID-19 and were admitted for an acute condition were not screened for infection with SARS-CoV-2 prior to admission and were admitted to one of the general wards. All other patients were screened for SARS-CoV-2 infection; those who tested positive were admitted to the COVID-19 ward. Patients suspected of having COVID-19 but testing negative by RT-PCR were admitted to the COVID-19 ward but were isolated from patients with a confirmed diagnosis of COVID-19 and underwent a second RT-PCR test. If the second test was negative, the patient was transferred to one of the general wards; because of the shortage of beds in the hospital, some such patients had to remain on the COVID-19 ward. Any HCW who presenting with COVID-19 symptoms was put on leave and allowed to return to work after three days if a subsequent RT-PCR test was negative. If a patient on a general ward was suspected of having COVID-19 and tested positive, all of the patients on that ward were screened by RT-PCR, and all of the HCWs in charge of the index patient would be tested but were put on leave only if they tested positive.

For in patients in whom RT-PCR yielded a positive result for SARS-CoV-2, epidemiological and clinical data were collected from the electronic medical records, in order to identify those with in-hospital transmission of COVID-19. The data collected included age, sex, self-reported skin color, comorbidities, reason for admission, length of hospital stay, and the time from admission to the identification of SARS-CoV-2 infection, as well as information related to the circumstances of the discovery of infection (contact tracing or report of an outbreak in a sector) and the clinical course of the disease.

To define cases of nosocomial transmission of SARS-CoV-2, we applied the criteria established by the Brazilian National Health Regulatory Agency,[13] which defines nosocomial transmission of SARS-CoV-2 as that occurring after a hospital stay of more than 14 days or after a hospital stay of more than 7 days in a patient exposed to a confirmed case of COVID-19, be it another patient sharing the room (close contact for more than 24 hours) or an HCW with COVID-19 RT-PCR in charge of patient. We also evaluated readmissions for COVID-19 within the first 7 days after discharge.

When SARS-CoV-2 infection was identified more than 14 days after hospital admission, it was classified as nosocomial infection. When such infection was identified between day 7 and day 14 of hospitalization, it was classified as possible nosocomial infection. Among patients who had been hospitalized for at least 7 days and were readmitted for COVID-19 within the first 7 days after discharge, such infection was also classified as a possible nosocomial infection.

The study was approved by the Research Ethics Committee of the Hospital São Paulo (Ruling nos. 4.264.650 and 37048020.3.0000.5505). Because of the retrospective nature of the study, the requirement for written informed consent was waived.

Statistical analysis

The descriptive analysis was based on the calculation of the absolute and relative frequencies of the clinical and sociodemographic variables studied, as well as the mean values with ranges or standard deviations. The incidence density of nosocomial SARS-CoV-2 infection was calculated as follows:

Incidence density = number of infections / patient-days per month $\times$ 1.000

Data were analyzed with the STATA statistical software package, version 16 (Stata Corp, College Station, TX, USA), and the graphic was prepared with GraphPad Prism, version 9 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Between March 1, 2020 and February 28, 2021, SARS-CoV-2 was identified by RT-PCR in the respiratory secretions of 2,146 patients who had been admitted to the Hospital São Paulo. Of those 2146 patients, 185 (8.6%) were classified as cases of nosocomial infection or as a possible nosocomial infection. Those 185 cases are described in Table 1.

Of the 185 cases of SARS-CoV-2 nosocomial infection or possible SARS-CoV-2 nosocomial infection, 179 (96.8%) occurred on the general hospital wards (Fig1), translating to an annual incidence density of 1.7 cases per 1.000 patient-days. Only 6 cases (3.2%) occurred on the wards dedicated to the treatment of patients infected with SARS-CoV-2, the annual incidence density for those wards being 0.1 cases per 1.000 patient-days.

Table 1
Distribution of cases of in-hospital transmission of SARS-CoV-2. Hospital São Paulo, March 2020 to February 2021

Variable	n (%)
Sex	
Male	115 (62.1)
Female	70 (37.8)
Self-reported skin color	
White	97 (52.4)
Brown	68 (36.7)
Black	18 (9.7)
Yellow	2 (1.1)
Age, years	
0-19	2 (1.1)
20-39	29 (15.6)
40-59	56 (30.2)
60-79	80 (43.2)
≥ 80	18 (9.7)
Comorbidities	
Diabetes mellitus	58 (31.3)
Heart failure	4 2 (22.7)
Nephropathy	42 (22.7)
Liver disease	31 (16.7)
Neoplasia	28 (15.1)
Lung disease	17 (9.1)
Cerebrovascular disease	15 (8.1)
Vascular disease	11 (5.9)
Acquired immunodeficiency syndrome	10 (5.4)
Acute myocardial infarction	7 (3.7)
Hemiplegia	3 (1.6)
Connective tissue disease	1 (0.5)
Admission diagnosis	
Circulatory system disease	48 (25.9)
Infectious or parasitic disease	40 (21.6)
Disease of the genitourinary tract	22 (11.9)
Disease of the respiratory tract	16 (8.6)
Injury or other consequences of external forces	15 (8.1)
Disease of the digestive tract	14 (7.6)
Neoplasia	10 (5.4)
Endocrine disease	5 (2.7)
Hematopoietic disease	4 (2.2)
Disease of the skin or subcutaneous tissue	4 (2.2)
Other	7 (3.7)
Charlson comorbidity index	
0	17 (9.1)
1-2	44 (23.7)
3-4	56 (29.7)
> 4	68 (36.7)

The distribution of cases among the most relevant inpatient wards for patients without COVID-19 and their respective incidence densities are shown in Table 2. The incidence density was found to be highest for the cardiac surgery ward (12.16 cases per 1000 patient-days), whereas it was 6.65 cases per 1000 patient-days for the semi-intensive care unit and 6.10 cases per 1000 patient-days for the male internal medicine ward.

Of the 185 cases of SARS-CoV-2 nosocomial infection or possible SARS-CoV-2 nosocomial infection, 115 (62.2%) were in men. The mean age of the patients evaluated was 58.3 years (range: 0-92 years). Of the patients evaluated, 97 (52.4%) self-reported their skin color as White.[14] The main diagnoses that prompted the hospitalization of those patients were diseases of the circulatory system, in 48 (25.9%); infectious and parasitic diseases, in 40 (21.6%); and diseases of the genitourinary system, in 22 (11.9%). Additional admission diagnoses are presented in Table 1. One hundred-fifty patients (81.1%) had at least one comorbidity, the most prevalent being diabetes, in 58 (31.4%); chronic kidney disease, in 42 (22.7%); and heart failure, in 42 (22.7%). Other comorbidities are shown in Table 1. We also calculated the Charlson comorbidity index for all patients and found it to be 0 in 17 cases (9.1%), 1-2 in 44 (23.7%), 3-4 in 56 (29.7%); and > 4 in 68 (36.7%).

Of the 185 cases of SARS-CoV-2 nosocomial infection or possible SARS-CoV-2 nosocomial infection, 140 (75.7%) were identified after day 14 of hospitalization and were therefore classified as cases of confirmed nosocomial infection, whereas 45 (24.3%) were identified between day 7 and 14, therefore being classified as cases of possible nosocomial infection. In 167 cases (90.3%), the patients were admitted to the hospital only once during the study period. Among those cases, the mean hospital stay was 36.2 days (range: 10-170 days). In the remaining 18 cases (9.7%), COVID-19 was diagnosed after discharge. The mean length of hospital stay was 21.6 days (range: 8-39 days) and 18.9 days (range: 1-55 days) in the first and second admissions, respectively. On average, symptoms appeared 1.8 days after discharge (range: 1-3 days) and the time from discharge to readmission was 2.9 days (range: 1-6 days).

Thirty-five patients (18.9%) remained asymptomatic throughout their hospital stay. Of those 35 patients, 22 (62.8%) underwent screening for SARS-CoV-2 infection because there was a report of close contact with a confirmed case sharing the same room. The remaining 13 patients (37.1%) they were screened because of an increased number of cases in the ward. We identified no transmission from an HCW to a patient. Among those 13 patients, the mean hospital stay was 33.6 days (range: 15-63 days), their cases therefore meeting the criteria for nosocomial infection.

In the sample as a whole, the main symptoms were dyspnea, in 104 (56.2%); cough, in 65 (35.1%); and fever, in 57 (30.8%). Those and other symptoms are reported in Table 1. Among the 150 patients who developed symptoms, nosocomial infection with SARS-CoV-2 was defined by the relationship between the onset of symptoms and the report of close contact with a confirmed case in 62 (41.3%) and by symptom onset only in 88 (58.7%). The mean time from hospital admission to symptom onset was 31.8 days (range: 7-939 days).

Oxygen therapy was required in 149 (80.5%) of the 185 cases evaluated. Among those 149 cases, invasive mechanical ventilation was required in 91 (61.1%) and the mean time on mechanical ventilation was 13 ± 10.9 days. In 5 (2.7%) of the 185 cases, the initial symptom was acute respiratory failure and the patients were promptly intubated. All of the patients who required mechanical ventilation received some type of vasoactive drug, and the mean duration of vasoactive drug use was 12.8 ± 11.8 days).

Of the 185 patients evaluated, 125 (67.5%) were admitted to the intensive care unit (ICU), and the mean ICU stay was 13.6 ± 13.3 days. Twenty-one (16.8%) of those patients were readmitted, and the mean ICU stay during the second hospitalization was 15.6 ± 12.3 days.

The outcome was discharge in 81 cases (43.7%) and death in 104 (56.2%). Among the patients who died, the mean time from the diagnosis of COVID-19 to death was 19.1 ± 23.3 days.

DISCUSSION

Here, we have described a cohort of patients who developed nosocomial infection with SARS-CoV-2 during the COVID-19 pandemic on general inpatient wards and on wards reserved for patients with suspected or confirmed SARS-CoV-2 infection. To our knowledge, this study is the first to report the incidence density of nosocomial infection with SARS-CoV-2 at a large hospital and by inpatient ward. It is noteworthy that the in-hospital incidence of infection with SARS-CoV-2 was higher than the incidence in the community during the same period.[2]

In our sample, there was a predominance of men, and the mean age was 58.3 years. Most previous studies of this topic have analyzed smaller numbers of cases, have reported differences between the sexes, and have evaluated patient samples with lower mean ages.[6-10,12,15]

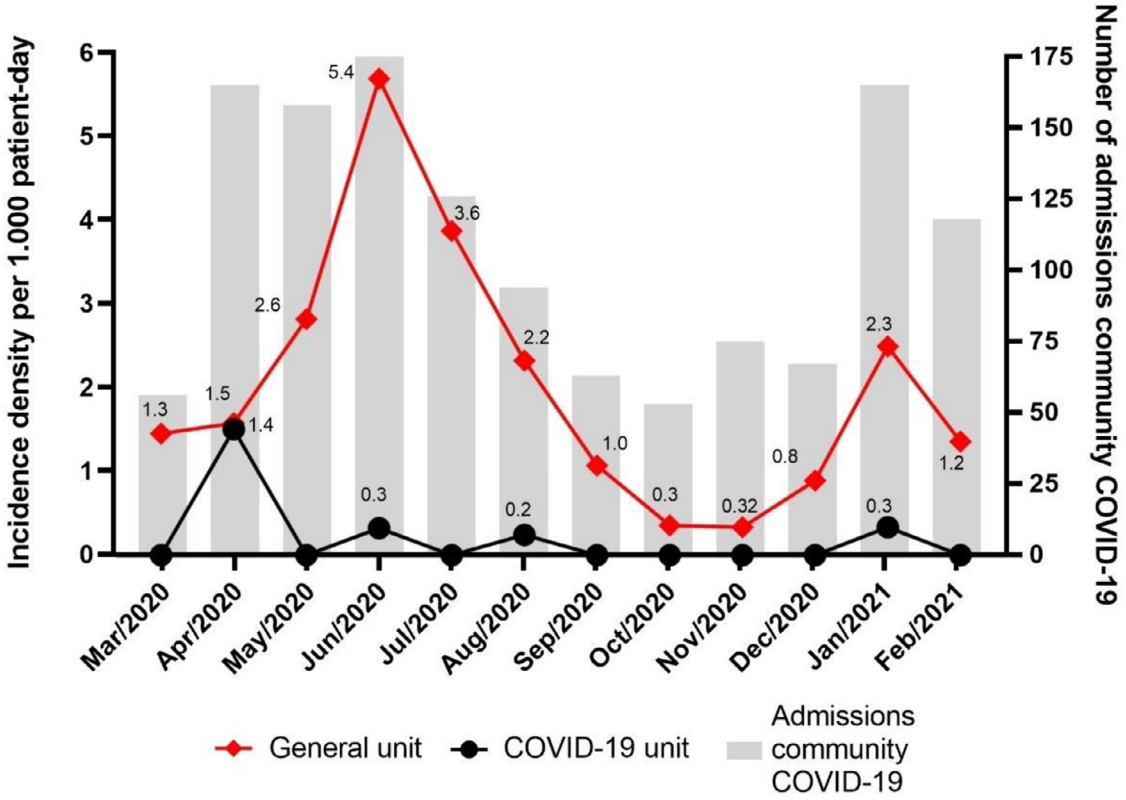

Fig. 1. Monthly distribution of the incidence density of in-hospital transmission of SARS-CoV-2. Hospital São Paulo, March 2020 to February 2021.

The sociodemographic data collected in the present study are proportional to those of individuals infected with SARS-CoV-2 in the general population of Brazil, as reported by the Brazilian National Ministry of Health.[2]

One of the main steps in defining cases of nosocomial infection with SARS-CoV-2 is ruling out previous infection at hospital admission. The diagnosis at admission facilitates the scaling of patients among the hospital wards. In the present study, most of the patients had admission diagnoses unrelated to SARS-CoV-2 infection. Other studies of this topic have reported similar patient profiles at hospital admission.[6-9]

There are several possible routes of transmission of SARS-CoV-2 in hospital settings. Prolonged hospitalization increases the risk of infection by viral dissemination from suspected or confirmed cases, because the incidence of SARS-CoV-2 infection can be high, especially in extra-hospital settings, exposing HCWs and family members, who can contribute to the rapid spread of the virus in the hospital environment.[16,18] Most of the patients in our study remained in the hospital longer than what is defined as the maximum viral incubation period and longer than what has been reported in some other studies.[9,12,16,17] In the cases in which the hospital stay was shorter, a report of close contact with a confirmed case or of an increased number of cases on a specific ward facilitated the identification of cases.

To our knowledge, this is the first study of its type to evaluate cases of hospital readmission, including the calculation of the time between exposure and the onset of symptoms. In all of the cases of readmission evaluated in our study, the mean time from the initial discharge to symptom onset was 1.8 days.

It is not always possible to screen all inpatients for infection or to identify the routes of transmission, especially when there is a considerable increase in the numbers of suspected or confirmed (mild-to-moderate or severe) cases that require hospital admission. It should be borne in mind that the hospital studied continued to serve the general population, accepting hospitalizations from various medical specialties, throughout the study period, which lessened the traceability of suspected or confirmed cases, as has previously been reported.[7,9-12,15,17] In most studies of this type, asymptomatic cases are rare or nonexistent, because of the limited number of respondents. In addition, some studies cite the timing of the onset of symptoms as one of the criteria for the definition of nosocomial infection. In studies evaluating samples that included asymptomatic patients, such patients have accounted for 4%-32% of cases,[6,15] which suggests that the 18.9% observed in our study sample is within the limits of normality.

The main symptoms reported in the studies analyzed were dyspnea, fever, and cough,[6,15] as was the case in our study. In other studies, the symptoms reported were characteristic of a common flu, all cases being classified as mild.[12,17] In one study, cases were classified simply as mild-to-moderate or severe.[7] Given the diversity of the signs and symptoms of infection with SARS-CoV-2, a more specific screening process is necessary. Protocols to screen for signs and symptoms, together with laboratory tests, should be implemented in order to avoid outbreaks of SARS-CoV-2 infection in the wards, because asymptomatic cases might account for a considerable

Table 2
Distribution of cases and incidence density of in-hospital transmission of SARS-CoV-2, by ward. Hospital São Paulo, March 2020 to February 2021

Ward	Nosocomial infection	Patient-days	Incidence density
Cardiac surgery	20	1645	12.16
Semi-intensive care	18	2708	6.65
Male internal medicine	24	3934	6.10
Cardiology	14	2770	5.05
Intensive care	12	2819	4.26
Organ transplant	9	2785	3.23
Other	88	1694	51.95

portion of such infections and the presymptomatic period could be essential to the transmission of the virus.[18]

In most of the cases evaluated in the present study, oxygen therapy and mechanical ventilation were required. In some of those cases, the disease was more severe, evolving to acute respiratory distress syndrome. In previous studies of nosocomial infection, those details have rarely been described. In some such studies, patients are stratified only by the need for medical care in general,[6,9] whereas in others they are classified as mild-to-moderate or severe cases.[7,15]

The mortality rate in our sample was higher than that reported in other studies.[6,17] However, the mortality rate is linked to the number of reported cases of nosocomial infection and the time of observation. Most previous studies have evaluated small numbers of cases and have not followed all of those cases to their final outcome.[8,9,17]

During the current pandemic, preventive measures were instituted to minimize the risk of contamination throughout the hospital: training of care and administrative teams; increased distribution of alcohol-based solutions for hand hygiene; and the systematic use of personal protective equipment. Protocols to screen for SARS-CoV-2 infection at admission were adopted. However, such screening has limitations due to the relatively long incubation period of COVID-19 and the low sensitivity of the RT-PCR tests, making it impossible to definitively rule out SARS-CoV-2 infection.

Despite the preventive measures taken, nosocomial transmission of SARS-CoV-2 occurred throughout our hospital. Therefore, such measures should be intensified when the incidence of community transmission peaks, because the overburdening of health care facilities favors in-hospital dissemination. It is of fundamental importance that the hospital infection control team maintain daily communication and organize continuing education sessions on the use of personal protective equipment for the prevention of COVID-19 outbreaks.

In the present study, the incidence density was higher for the general hospital wards, where there is often less concern on the part of HCWs, family members, and other people who circulate through. That provides favorable conditions for viral dissemination. Measures that facilitate the detection of suspected or confirmed cases, such as screening through laboratory tests and raising the awareness of HCWs of the need for the speedy identification of symptomatic cases, are excellent tools for the prevention of outbreaks. Because prolonged hospital stays increase the risk of nosocomial infection, including infection with SARS-CoV-2, patients who are well enough should be discharged promptly, in order to minimize that risk.

Our study has some limitations. Primarily, the lack of clinical information in some cases made the surveillance of SARS-CoV infections more difficult. There is a need for multicenter observational studies to identify groups at higher risk for nosocomial infection. The findings of such studies could improve patient care and promote the adoption of effective measures to control such infections.

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