



Risk factors for nosocomial bloodstream infections in COVID-19 affected patients: protocol for a case–control study

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ABSTRACT

Background Nosocomial bloodstream infection (nBSI) is an important clinical concern among COVID-19 hospitalised patients. It can cause sepsis and septic shock leading to high morbidity, mortality, and the emergence of antibiotic resistance. The aim of this case–control study is to identify the risk factors associated with the nBSI development in COVID-19 hospitalised patients and its incidence.

Methods and analysis A retrospective case–control study will be performed. Cases will include nBSI episodes of adult patients (≥ 18 years) admitted to Hospital Universitari Germans Trias i Pujol, Barcelona, Spain, from April to December 2020 with a diagnosis of SARS-CoV-2 pneumonia. Patients transferred from other hospitals will be excluded. Controls will include hospitalisation episodes of COVID-19 patients without nBSI. We will recruit a minimum of 74 nBSI episodes (cases) and 74 controls (according to sample size calculation). We will collect data on sociodemographics, clinical status at admission, hospital admission, in-hospital mortality, and exposure data (use of antivirals, glucocorticoids or immunomodulatory agents, length of hospitalisation, and use of medical devices such as intravenous catheters). A bivariate and a subsequent multivariate regression analysis will be performed to assess the independent effect of the associated risk factors after adjusting for confounders. The nBSI incidence rate will be estimated according to the number of nBSI episodes in admitted COVID-19 patients among the total person-month of follow-up.

Ethics and dissemination The protocol of this study was approved by the Ethical Committee for Drug Investigation of the Hospital Universitari Germans Trias i Pujol. The results of this case–control study will be published in a peer reviewed journal.

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is one of the biggest challenges undergone by health professionals around the world, being a public health emergency of international concern. From the first case reported in December 2019 in Wuhan, China, SARS-CoV-2 spread progressively to other countries, saturating hospitals throughout the world and leading to an unprecedented strain on hospital resources.^{1,2}

Hospitalised patients are susceptible to hospital-acquired infections such as bacterial bloodstream infections (BSIs).³ BSIs can cause sepsis and septic shock which can lead to high morbidity and mortality.^{4–7} A systematic review which aimed to estimate the total number of BSI episodes and related deaths per year in

North America and Europe showed that there were over 1.2 million BSI episodes that caused 157 000 deaths per year in Europe, based on studies performed in Denmark, England, and Finland.⁸ Nosocomial bloodstream infections (nBSI), which occur beyond the first 48 hours of hospitalisation, are associated with high mortality and healthcare resource consumption, especially in intensive care units (ICUs), and are one of the biggest clinical concerns regarding the quality of care and patient safety.^{4,5,9–13} Also, the emergence and spread of antibiotic-resistant bacteria are of great concern. Due to the emergence of antimicrobial resistance, treatment has become difficult, especially for infections caused by gram-negative bacteria, which can be serious and even fatal in hospitalised patients.^{14,15}

Moreover, recent studies have shown that the incidence of nBSI among COVID-19 patients admitted to an ICU is high and that it could be related to significant increases in length of ICU stay, and the need for invasive mechanical ventilation.^{16,17} This condition could be related to the immune dysregulation of severely affected patients, the need for extensive antimicrobial use, and less compliance with preventive measures.¹⁷ Commonly, nBSI has been associated with multiple risk factors in hospitalised patients such as admission to an ICU, prolonged hospitalisation, the need for mechanical ventilation, use of intravenous catheters, use of immunosuppressive drugs, presence of neutropenia or haematological or solid organ transplants, among others.^{3,18–25} Many of these risk factors are common clinical conditions among hospitalised patients with COVID-19.^{26–29} Furthermore, these patients are often exposed to prolonged antibiotic therapies and/or strong treatments with immunomodulators or anti-inflammatory drugs, which could be associated with nBSI.^{30–34}

Recently, numerous studies have been published to assess the clinical characteristics, demographics, mortality, and therapeutic outcomes in COVID-19 patients.^{26–28} However, little is still known about the risk factors for developing non-viral infections such as nBSI or the emergence of antimicrobial resistance in COVID-19 patients, which may participate in adversely influencing the outcome of any hospitalised patient.^{35,36}

Determining the incidence and risk factors for developing nBSI in hospitalised COVID-19 patients is a first step towards planning the appropriate strategies aimed to prevent this clinical complication and to be taken into consideration by healthcare professionals. The aim of this case–control study is to identify the



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risk factors associated with the development of nBSI in COVID-19 hospitalised patients and to determine its incidence.

METHODS AND ANALYSIS

A retrospective case-control study to assess the risk factors associated with the development of nBSI in COVID-19 hospitalised patients will be performed. Moreover, the incidence of nBSI among hospitalised patients with COVID-19 will be calculated.

This single centre study will be performed at Hospital Universitari Germans Trias i Pujol, a 650 bed tertiary teaching hospital near Barcelona, Spain, which assists over 800 000 inhabitants and which has provided medical assistance to >4500 COVID-19 affected patients.

Study sample

The study sample will include patients admitted to the Hospital Universitari Germans Trias i Pujol Hospital from April to December 2020 with a confirmed diagnosis of SARS-CoV-2 pneumonia. Patients will be included if they were adult patients (≥ 18 years) and excluded if they were transferred from other hospitalisation centres before admission. Positive COVID-19 patients admitted to the hospital during this period were those having at least one PCR test (polymerase chain reaction) positive for SARS-CoV-2 obtained from the nasopharynx and/or oropharynx sample, or a positive antigen rapid test detection from a nasopharynx sample.

Case and control identification

For cases, we will include all the nBSI episodes developed in patients complying with eligibility criteria during the period of study with a minimum of 74 episodes (according to sample size calculation).

These episodes are those in which patients presented positive blood cultures in a blood sample taken after 48 hours since hospital admission.³⁷ In the case of a blood culture positive for coagulase-negative staphylococci or other common skin bacteria, the presence of another consecutive positive blood culture for the same pathogen and/or the following clinical characteristics will be necessary: fever ($>37^{\circ}\text{C}$) and/or leukocytosis ($>11 \times 10^9/\text{L}$) and/or high inflammatory parameters such as C-reactive protein (CRP) ($\geq 3 \text{ mg/mL}$) or procalcitonin ($\geq 0.5 \text{ ng/mL}$).³⁷⁻⁴⁰ Cases in which the patient presents more than one positive blood culture for the same microorganism, but separated by ≥ 30 days, will be considered independent episodes of nBSI. In the case of patients affected by polymicrobial infections, an independent episode for each isolated microorganism will also be considered.

For controls, a minimum of 74 admission episodes (the same number as the cases and according to the sample size calculation) will be randomly selected in patients with COVID-19 and without nBSI who were admitted during the same period of time, and will be matched with the cases by date of admission (± 7 days) to homogenise the epidemiological situation, in-hospital treatment protocol and hospital pressure.

Data collection

A database will be created to record the variables to be obtained (Microsoft Excel Software, USA, 2010). A consecutive numerical value will be assigned to each patient, and with this coding they will be entered into the database created. In this way, the information recorded will be completely anonymous and will not contain any value that allows the study participants to be identified or traceability carried out. The identity of the patients will be protected and recorded on paper and only under the custody of the main researchers and collaborators, guaranteeing the security of the data

and avoiding any undue access of third parties. The following data will be obtained and recorded in the created database.

Demographic data and previous medical record: age in years, gender, comorbidities (number and Charlson index), diabetes mellitus, hypertension, chronic renal failure (defined as glomerular filtration rate $< 60 \text{ mL/min/1.73 m}^2$ ⁴¹), dialysis, solid cancer, haematological malignancy, neutropenia (defined as neutrophil blood count $\leq 1.5 \times 10^9/\text{L}$ ⁴²), solid organ transplants, HIV infection, liver disease (moderate to severe, including compensated or decompensated liver cirrhosis), colonisations and/or infections during the last year before hospital admission, and hospital admissions during the last year.

Specific data of the current admission and related to the nBSI: hospital admission date, admission units, surgeries during the current admission before nBSI, nBSI (origin, microorganism, and resistance mechanism), leucocyte blood count and CRP value (they were collected the day when the first positive blood culture was drawn), use of antibiotics before nBSI, the need for mechanical ventilation before nBSI, use of intravenous catheters before nBSI, use of interleukin-6 blockers (tocilizumab, sarilumab and siltuximab) before nBSI, antivirals against COVID-19 before nBSI, use of corticosteroids before nBSI, in-hospital mortality, and hospital discharge date.

Sample size and statistical analysis

Accepting an α risk of 0.05 and a β risk of < 0.2 in a unilateral contrast, it takes a minimum of 74 cases and 74 controls to detect a minimum odds ratio of 2.5. It is assumed that the exposure rate in the control group will be 0.5. A loss to follow-up rate of 0% has been estimated. The Poisson approximation has been used.

Patients' data will be registered in an electronic database in a way that is dissociated from any information that may allow the identification of the patient for subsequent purification and statistical analysis.

The statistical plan analysis will include:

- ▶ Descriptive analysis of the main characteristics of the study sample through means and standard deviations for the numerical variables and percentages for the categorical variables.
- ▶ Evaluation of the homogeneity between cases and controls. The numerical variables will be compared using the Student's t-test or the Mann-Whitney test and the categorical variables using the χ^2 or Fisher's exact test.
- ▶ Bivariate evaluation of the main factors associated with nBSI will be evaluated with the same statistical tests as in the previous section. The odds ratio (OR) and its 95% confidence interval (95% CI) will be considered as a measure of association, which will be estimated using logistic regression.
- ▶ A subsequent multivariate regression analysis will be performed to assess the independent effect of the associated risk factors after adjusting for confounders.
- ▶ The incidence rate of nBSI developed during the study period and its 95% CI will be estimated according to the number of new nBSI episodes in hospitalised patients with COVID-19 divided by the total person-month of follow-up (sum of the months follow-up of all patients with COVID-19 admitted from the moment of admission to the moment of nBSI or the moment of discharge).
- ▶ The incidence rate of nBSI developed from April to December 2019 and its 95% CI will be estimated according to the number of new nBSI episodes in hospitalised patients divided by the total person-month of follow-up (sum of the follow-up months of all patients from the moment

of admission to the moment of nBSI or the moment of discharge), and it will be compared with the COVID-19 patients' incidence using the χ^2 test.

- Analysis of nBSI-free survival in patients with COVID-19 using Kaplan-Meier tables, comparison of survival curves between various groups or risk factors with the log rank test, and Cox regression (bivariate and multivariate).

ETHICS AND DISSEMINATION

The results of this case-control study will be published in a peer reviewed journal. The protocol of this study was evaluated and approved by the Ethical Committee for Drug Investigation of the Hospital Universitari Germans Trias i Pujol (protocol code PI-21-047).

This project will be carried out in accordance with the basic principles of protection of the rights and dignity of the human being, as stated in the Declaration of Helsinki, and in accordance with current regulations. The General Data Protection Regulation (GDPR) of the European Union 2016/679 will be followed. The patients included in the study were not subjected to any experimental procedure.

The protocol for this case-control study is the first step towards establishing the relationship between some sanitary interventions and the occurrence of nBSI in hospitalised patients with COVID-19 disease. This research will be performed and reported following the recommendations stated in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies using the points applicable to case-control studies.⁴³

DISCUSSION

The protocol for this case-control study is the first step to assess the risk factors involved and the incidence of nBSI in hospitalised COVID-19 affected patients. This important clinical concern has been previously addressed in some recent studies. Nevertheless, there is still some controversy in the available evidence both in the risk factors involved and in the incidence of nBSI in this population. Therefore, our purpose is to perform the first study aimed to evaluate these conditions over a longer period of time, including patients affected by two COVID-19 waves in Spain (from April to December 2020).

A retrospective single centre study performed in 226 hospitalised patients with COVID-19 in the USA showed a significantly higher rate of both bacterial (25% vs 13.1%, $p=0.041$) and fungal (12.7% vs 0.7%, $p<0.001$) infections in those patients treated with steroids. A subgroup analysis denied a significant effect of tocilizumab on the occurrence of these infections.⁴⁴ Similarly, a case-control study performed in 100 hospitalised patients with COVID-19 in Pakistan showed that the treatment with systemic steroids was an independent risk factor for the development of bacterial infections (OR 4.60, 95% CI 1.24 to 17.05), but this effect was not described for treatments with tocilizumab or antibiotics.⁴⁵ Furthermore, a study performed in critically ill patients with COVID-19 in Italy showed an independent association between anti-inflammatory treatments (cause-specific hazard ratio (csHR) 1.07, 95% CI 0.38 to 3.04 for tocilizumab, csHR 3.95, 95% CI 1.20 to 13.03 for methylprednisolone, and csHR 10.69, 95% CI 2.71 to 42.17 for methylprednisolone plus tocilizumab) and the development of BSI.³⁵ However, a prospective matched case-cohort study performed in France, which included patients admitted to an ICU requiring ventilation due to acute respiratory distress syndrome (235 patients with COVID-19 and 235 without) showed a significantly increased risk in those patients treated with tocilizumab or anakinra (sHR 3.20, 95% CI 1.31 to 7.81; $p=0.011$), but not with corticosteroids.⁴⁶

Other studies dealt with this issue without assessing the effect of drugs commonly used in COVID-19 patients. A study performed in China showed that white blood cell count (>10 or $\leq 4 \times 10^9/L$, OR 8.38, 95% CI 1.07 to 65.55), procalcitonin (>0.1 ng/mL, OR 4.92, 95% CI 1.39 to 17.33) and the presence of urinary catheterization (OR 25.38, 95% CI 5.09 to 126.53) before the infectious episode were independent risk factors for nosocomial bacterial infections in patients with COVID-19, after adjusting for age and use of a ventilator and venous catheterization.⁴⁷ Another study performed in 227 hospitalised patients with COVID-19 in Copenhagen showed that lower peripheral oxygen saturation, oxygen supplementation or mechanical ventilation, lower lymphocyte count, and elevated plasma lactate dehydrogenase and CRP were associated with the BSI development.³⁴

The incidence of nBSI in COVID-19 affected patients has also been assessed in some studies showing a high variability that depended on the context and the methodology used. A study conducted in Italy on 89 COVID-19-affected patients admitted to the ICU showed a high frequency of BSI (60 affected patients, 67.4%). Moreover, significantly higher frequencies were reported in the period between 21 February 2020 and 30 April 2020 (87/1000 days of ICU stay, 95% CI 67 to 112) than that during the same period in 2018 (24/1000 days of ICU stay, 95% CI 11 to 54) or 2019 (19/1000 days of ICU stay, 95% CI 8 to 45; $p<0.001$).¹⁶ Similarly, another study performed in Italy found that from 57 COVID-19 patients admitted to an ICU, BSI occurred in 49% of them with an incidence rate of 373 per 10000 patient-days.¹⁷ However, a study performed in Sweden detected a clinically relevant microbial growth in blood cultures in 6.5% of COVID-19-affected patients, which was significantly lower compared with 10.8% in the 2020 control group without COVID-19 ($p<0.0001$) and 10.4% in the 2019 control group without COVID-19 ($p<0.0001$).⁴⁸ These data coincide with a study conducted in the USA which found that the blood culture positivity rate was significantly lower for patients who tested positive for SARS-CoV-2 when compared with those who did not and to those who were not tested (3.8%, 8.0% and 7.1%, respectively; $p<0.001$).⁴⁹

A rapid systematic review of 24 studies (3338 hospitalised paediatric and adult COVID-19 affected patients), that aimed to assess the available literature on the prevalence of bacterial infections in COVID-19 affected patients, showed that 3.5% (95% CI 0.4% to 6.7%) and 14.3% (95% CI 9.6% to 18.9%) of these patients suffered a bacterial co-infection or secondary infection, respectively, and that this was more common in those patients who were critically ill (8.1%, 95% CI 2.3% to 13.8%).⁵⁰ A systematic review and meta-analysis of 30 studies performed by Lansbury *et al* showed that 7% (95% CI 3% to 12%, $n=2183$, data from 18 studies and 19 datasets) of COVID-19 hospitalised patients had laboratory-confirmed bacterial co-infections.⁵¹

The evidence presented to date is inconclusive since different risk factors and different effects of the drugs used to treat COVID-19 on the presence of nBSI have been described. This study will be of interest to know in-depth what the reality has been in our surrounding area, a teaching university hospital with over 650 beds near Barcelona (900 beds during the COVID-19 pandemic), which has given medical attention to more than 4500 COVID-19 affected patients.

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All authors contributed to the performance of this protocol and read and approved the final version of this manuscript.

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