# Incidence, risk factors, and outcome of suspected central venous catheter-related infections in critically ill COVID-19 patients: a multicenter retrospective cohort study

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# INCIDENCE, RISK FACTORS, AND OUTCOME OF SUSPECTED CENTRAL VENOUS CATHETER-RELATED INFECTIONS IN CRITICALLY ILL COVID-19 PATIENTS: A MULTICENTER RETROSPECTIVE COHORT STUDY

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ABSTRACT—**Background:** Aims of this study were to investigate the prevalence and incidence of catheter-related infection, identify risk factors, and determine the relation of catheter-related infection with mortality in critically ill COVID-19 patients. **Methods:** This was a retrospective cohort study of central venous catheters (CVCs) in critically ill COVID-19 patients. Eligible CVC insertions required an indwelling time of at least 48 hours and were identified using a full-admission electronic health record database. Risk factors were identified using logistic regression. Differences in survival rates at day 28 of follow-up were assessed using a log-rank test and proportional hazard model. **Results:** In 538 patients, a total of 914 CVCs were included. Prevalence and incidence of suspected catheter-related infection were 7.9% and 9.4 infections per 1,000 catheter indwelling days, respectively. Prone ventilation for more than 5 days was associated with increased risk of suspected catheter-related infection; odds ratio, 5.05 (95% confidence interval 2.12–11.0). Risk of death was significantly higher in patients with suspected catheter-related infection (hazard ratio, 1.78; 95% confidence interval, 1.25–2.53). **Conclusions:** This study shows that in critically ill patients with COVID-19, prevalence and incidence of suspected catheter-related infection are high, prone ventilation is a risk factor, and mortality is higher in case of catheter-related infection.

KEYWORDS—Central venous catheters, catheter-related infections, COVID-19, intensive care



## INTRODUCTION

Central venous catheter (CVC) use is indispensable for clinical practice in intensive care units (ICUs). Adverse effects can complicate CVC use and may be mechanical, thrombotic, or infectious in origin (1,2). Catheter-related bloodstream infections are known to increase mortality risk and healthcare costs (3,4).

Central venous access can be obtained via either internal jugular, subclavian, or femoral veins. Insertion site in ICU patients is selected based on the expertise of the physician, patient's anatomy, and indication for CVC placement. Advantages of internal jugular and femoral vein cannulation are the possibility of ultrasound guidance and a small risk of mechanical complications, whereas subclavian vein cannulation is more patient-friendly and poses a smaller infection and thrombosis risk (5).

Since the emergence of coronavirus disease 2019 (COVID-19), many ICUs have been engulfed by critically ill patients. Shortages of personal protective equipment and increasing numbers of patients have put pressure on infection control practices. For patients with COVID-19, the odds to develop catheter-associated bloodstream infections are increased as compared with non–COVID-19 patient (6,7).

Many of these critically ill COVID-19 patients undergo prone ventilation to improve lung recruitability, homogenous ventilation, and oxygenation. Prone ventilation is a possible contributor to the increased rate of bloodstream infections (8). In prone position, CVC insertion site inspection and maintenance are more difficult. In addition, pooling of oral, nasal, and tracheal secretions at the internal jugular insertion site often leads to visible contamination.

It is yet unclear how many critically ill patients with COVID-19 exactly develop catheter-related infections, what risk factors are associated with catheter-related infections, and whether they are associated with an increased mortality. The aims of this study were, therefore, to estimate the incidence, to identify risk factors, and to investigate the association with mortality.

## MATERIALS AND METHODS

### *Study design and setting*

This was a retrospective cohort study on CVCs in critically ill COVID-19 patients admitted to 25 ICUs in the Netherlands between February 20, 2020, and March 2, 2021. Eligible patients were identified using "The Dutch Data Warehouse against COVID-19" (DDW), a large multicenter database of critically ill COVID-19 patients. This is a full-admission electronic health record database of 25 Dutch hospitals of 3,463 patients with more than 200 million data points (9). Patients in the database were admitted between February 20, 2020, and March 2, 2021. The institutional review board of Amsterdam UMC location Vumc waived the need for informed consent from individual patients and approved of an opt-out procedure. Current study results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (10).

### *Study population*

The study objects of interest consisted of CVCs in critically ill adult patients admitted to the ICU with COVID-19 pneumonia and a minimal indwelling time of 48 hours. Coronavirus disease 2019 positivity was defined by a positive result of a reverse transcription polymerase chain reaction assay for SARS-CoV-2. During ICU stay, a patient could undergo multiple CVC insertions and all CVCs placed in the internal jugular, subclavian, or femoral vein were included. In other words, the unit of analysis is the CVC clustered within critically ill COVID-19 patients. Central venous catheters without available insertion or removal dates were excluded. Central venous catheters from patients who died or were discharged before CVC removal were excluded as well.

### *Data collection and study definitions*

From the DDW age, sex, body mass index (BMI), length of ICU stay, CVC indwelling time, prone ventilation, insertion site, antibiotic use, corticosteroid use, Acute Physiology and Chronic Health Evaluation II score at time of CVC insertion, Sequential Organ Failure (SOFA) score at time of CVC removal, C-reactive protein (CRP), and procalcitonin were collected. Infectious complications of central venous catheterization are defined by diverse definitions. The criterion standard is a catheter-related bloodstream infection, defined as a positive catheter tip culture with the same microorganism cultured in peripheral blood or a differential time to positivity of more than 120 minutes between central venous and peripheral blood cultures with the same microorganism (11,12). Although guideline-based practice also includes blood culture testing in case of suspected bloodstream infection (13), microbiological data within such a definition may lead to underestimation of the incidence of catheter-related infections (11). Because microbiological data were unavailable in the DDW, 2 definitions for catheter-related infection were tested and they will be referred to as suspected catheter-related infection. First, because antibiotic administration is well recorded in the DDW, we used antibiotic use surrounding CVC removal as a surrogate measure for catheter-related infection. A suspected catheter-related infection was deemed present in case of starting vancomycin, gentamicin, flucloxacillin, or piperacillin/tazobactam 12 hours before CVC removal until 48 hours after CVC removal. These antibiotics were chosen as they covered most common causative microorganisms for catheter-related infections, that is, gram-positive cocci and gram-negative bacilli (13). To increase specificity, third-generation cephalosporins were excluded because these are often routinely administered in the context of selective decontamination of the digestive tract or empirically started in case of a suspected bacterial pulmonary superinfection in the Netherlands (14,15). In case of death or discharge before CVC removal, patients were regarded not to have developed catheter-related infection. Second, for a sensitivity analysis, we assessed an "inflammatory marker" definition of suspected catheter-related infection: a procalcitonin of at least 0.5 ng/mL at time of CVC removal and a CRP decrease of more than 50 mg/L within 5 days after CVC removal. A procalcitonin lower than 0.5 ng/mL has a good negative predictive value in a critically ill population (16). Delta CRP was added to increase specificity.

### *Outcomes*

Study outcomes were prevalence and incidence of suspected catheter-related infection, risk factors for suspected catheter-related infection, and survival of critically ill COVID-19 patients with a suspected catheter-related infection. Incidence was measured as the number of catheter-related infections per 1,000 catheter days. Hypothesized risk factors were age, sex, BMI, length of ICU stay, CVC indwelling time, insertion site, corticosteroid use, disease severity as measured by the Acute Physiology and Chronic Health Evaluation II score at time of CVC insertion, and days in prone ventilation during an indwelling CVC. Survival was measured

at day 28 of follow-up after CVC removal. Central venous catheters were right censored in case of hospital discharge or, if that date was not available, ICU discharge. Hazard ratios were adjusted for age, BMI, length of ICU stay, corticosteroid use, and SOFA score at time of CVC removal.

### *Statistical analysis*

Categorical variables are expressed as numbers and percentages. Continuous data were expressed as mean ± standard deviation (SD) or interquartile range. Normality of continuous variables was assessed by Q-Q plots and histograms. Risk factors were identified using a logistic regression model. Risk factors identified in the univariable model with a $P$ value of less than 0.10 were forwarded in the multivariable model. To avoid multicollinearity, correlations between all variables were tested and in case of a positive or negative Spearman correlation of 0.70 or greater, only the variable with the highest univariable association was retained. Because of nonlinearity of prone ventilation with the logit of the outcome, prone ventilation was categorized into the following: no prone ventilation, 0–5 days, and more than 5 days prone ventilation. A log rank test and multivariable proportional hazard model were used to assess survival. In all analyses, the CVC was the statistical unit of analysis. This means that patients who received multiple CVCs were included multiple times. To adjust for the lack of independence between observations, a robust sandwich covariance estimate was used to construct the 95% confidence intervals (CIs). Two sensitivity analyses were performed. The first comprised a subsample survival analysis that included one randomly selected CVC per patient. Furthermore, to check the robustness of our initial suspected catheter-related infection definition, a second sensitivity analysis consisted of a survival analysis using the alternative definition for CVC infection. Analyses were performed in Python *via* Jupyter Notebooks and R *via* Rstudio.

## RESULTS

Data on CVC use was available in five out of the 25 ICUs, resulting in a total of 815 patients. A total of 1,112 CVCs in 604 patients were eligible for inclusion. In 11 placements, no CVC removal date time was available and these were excluded. Of the remaining 1,101 CVCs, 187 had an indwelling time of less than 48 hours and were also excluded. In total, 914 CVC placements in 538 unique patients were included (Fig. 1). Baseline characteristics are described in Table 1. No significant difference was found between age, sex, and BMI. Of the 914 CVCs, 72 (7.9%) were complicated by a suspected catheter-related infection. The incidence of catheter-related infection was 9.4 per 1,000 catheter indwelling days. The median age was 66 (interquartile range, 58.5–72.0), 77.4% were male, and most had a CVC in the internal jugular vein (79.0%).

Table 2 shows the logistic regression analysis on potential risk factors for catheter-related infection. Univariably, ICU length of stay (OR per 1-day increase, 0.96; 95% CI, 0.94–0.98) and indwelling time (OR per 1-day increase, 0.97; 95% CI, 0.93–1.0) were negatively associated with suspected catheter-related infection. Prone ventilation was positively associated with suspected catheter-related infection (OR for 0- to 5-day prone ventilation, 2.52; 95% CI, 1.22–5.26, and OR for more than 5 days prone ventilation: 4.44, 95% CI, 2.12–9.29). In the multivariable analysis, only prone ventilation for more than 5 days remained associated with suspected catheter-related infection (OR, 5.05; 95% CI, 2.12–11.0).

In 24 CVC placements, there were no data available regarding discharge or death and these were excluded from the survival analysis. Moreover, during 206 CVC placements, the patient died (n = 164) or was discharged (n = 42) before removal of the CVC, leaving 684 CVCs for the survival analysis. Survival curves are depicted in Figure 2. Of 684 CVC placements, 72 (10.5%) were complicated by a suspected catheter-related infection. Survival

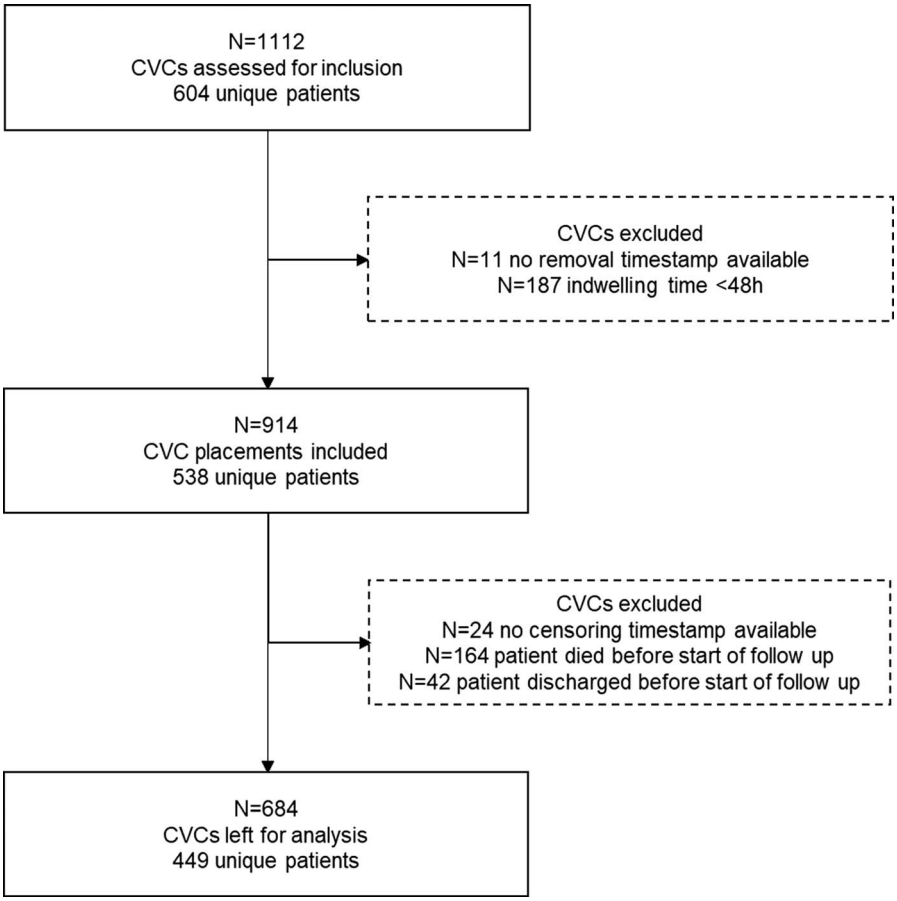


FIG. 1. **Consort flow diagram for included central venous catheters**. CVC, central venous catheter.

TABLE 1. **Population characteristics**

| Population characteristics* | Total, n (%), mean (SD), median (IQR) | No CRI, n (%), mean (SD), median (IQR) | CRI, n (%), mean (SD), median (IQR) | *P* |
|---|---|---|---|---|
| Total, n | 914 | 842 | 72 | |
| Age, y | 66 (58.5, 72.0) | 66 (58–72) | 66 (60–73) | 0.439 |
| Sex, n | | | | 0.090 |
| Male | 702 (77.4) | 640 (76.6) | 62 (86.1) | |
| Female | 205 (22.6) | 195 (23.4) | 10 (13.9) | |
| BMI, kg/m$^2$ | 26.8 (23.8–29.9) | 26.8 (23.8–30.0) | 26.3 (23.8–28.9) | 0.241 |
| Insertion site, n | | | | 0.900 |
| Internal jugular | 722 (79.0) | 666 (79.1) | 56 (77.8) | |
| Femoral | 149 (16.3) | 136 (16.2) | 13 (18.1) | |
| Subclavian | 43 (4.7) | 40 (4.8) | 3 (4.2) | |
| APACHE-II score at time of CVC insertion | 21.12 (4.15) | 21.09 (4.21) | 21.39 (3.42) | 0.594 |
| Length of ICU stay | 11.3 (6.8–20.6) | 11.7 (6.9–21.1) | 9.7 (6.5–12.4) | 0.010 |
| Corticosteroid use, n | 416 (45.5) | 388 (46.1) | 28 (38.9.0) | 0.292 |
| CVC indwelling time, d | 6.9 (4.8–10.10) | 6.9 (4.7–10.2) | 7.9 (5.7–9.2) | 0.704 |
| C-reactive protein†, mg/L | 115.50 (48.67–204.25) | 105.5 (43.5–186.3) | 225.5 (161.0–325.5) | <0.001 |
| SOFA-score† | 6.04 (3.18) | 5.94 (3.21) | 7.12 (2.63) | 0.003 |
| Prone ventilation‡, d | 1.7 (0.0–5.1) | 1.6 (0.0–4.8) | 4.3 (1.1–6.8) | <0.001 |

*Number in the table are number of CVCs; therefore, some patients are included more than once in the table.
†At time of central venous catheter CVC removal or discharge with CVC *in situ*.
‡Number of days in prone position during indwelling CVC.
APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CVC, central venous catheter; CRI, catheter-related infection; ICU, intensive care unit; IQR, interquartile range; SOFA, sequential organ failure assessment; SD, standard deviation.

was statistically different when comparing CVCs with and without a catheter-related infection (log rank: $P < 0.0001$). Table 3 shows hazard ratios regarding mortality. Risk of death at 28 days after CVC removal was significantly higher after suspected catheter-related infection; crude hazard ratio (2.50; 95% CI, 1.69–3.40, adjusted hazard ratio, 1.78; 95% CI, 1.25–2.53). Age, BMI, and SOFA score were positively associated with mortality, whereas length of ICU stay was negatively associated with mortality. Corticosteroid use was not associated with mortality.

Results of 2 sensitivity analyses are depicted in Figure 3. Figure 3(A) illustrates survival curves of a subsample sensitivity analysis that included one randomly selected CVC per patient. Of the 390 at risk patients, 29 (7.44%) developed a suspected catheter-related infection. Survival was statistically different when comparing CVCs complicated and not complicated by a suspected catheter-related infection (log rank: $P = 0.00017$). Figure 3(B) depicts survival curves of a sensitivity analysis using an alternative definition for catheter-related infection. Of the 544 at risk CVCs, 45 (8.27%) had a suspected catheter-related infection. Survival was statistically different when comparing CVCs with and without a suspected catheter-related infection (log rank: $P = 0.00041$).

## DISCUSSION

Main findings of this retrospective cohort study are (1) prevalence and incidence of suspected catheter-related infections in

TABLE 2. **Risk factors for suspected catheter-related infection**

| Variables | Univariable OR (95% CI) | *P* | Multivariable OR (95% CI) | *P* |
|---|---|---|---|---|
| Age, per year increase | 1.0 (0.98–1.03) | 0.622 | | |
| Sex | | | | |
| Male | Ref | 0.071 | Ref | 0.126 |
| Female | 0.53 (0.27–1.06) | | 0.57 (0.28–1.17) | |
| BMI, per kg/m$^2$ increase | 0.96 (0.92–1.00) | 0.057 | 0.95 (0.91–1.00) | 0.050 |
| Length of stay, per day increase | 0.96 (0.94–0.98) | 0.002 | 0.97 (0.93–1.01) | 0.108 |
| Indwelling time, per day increase | 0.97 (0.93–1.00) | 0.023 | 0.94 (0.88–1.01) | 0.104 |
| Corticosteroid use | 0.75 (0.45–1.22) | 0.242 | | |
| Prone ventilation | | | | |
| No prone ventilation | ref | | ref | |
| 0–5 d | 2.52 (1.22–5.26) | 0.012 | 2.04 (0.96–4.32) | 0.063 |
| > 5 d | 4.44 (2.12–9.29) | <0.001 | 5.05 (2.12–11.0) | <0.001 |
| APACHE-II-score, per point increase | 1.02 (0.97–1.07) | 0.524 | | |
| Insertion site | | | | |
| FV | ref | | | |
| IJV | 0.88 (0.47–1.66) | 0.692 | | |
| SV | 0.78 (0.21–2.97) | 0.721 | | |

Confidence intervals are robust intervals taking multiple CVCs per patient into account.
APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CI, confidence interval; CVC, central venous catheter; FV, femoral vein; IJV, internal jugular vein; OR, odds ratio; SV, subclavian vein.

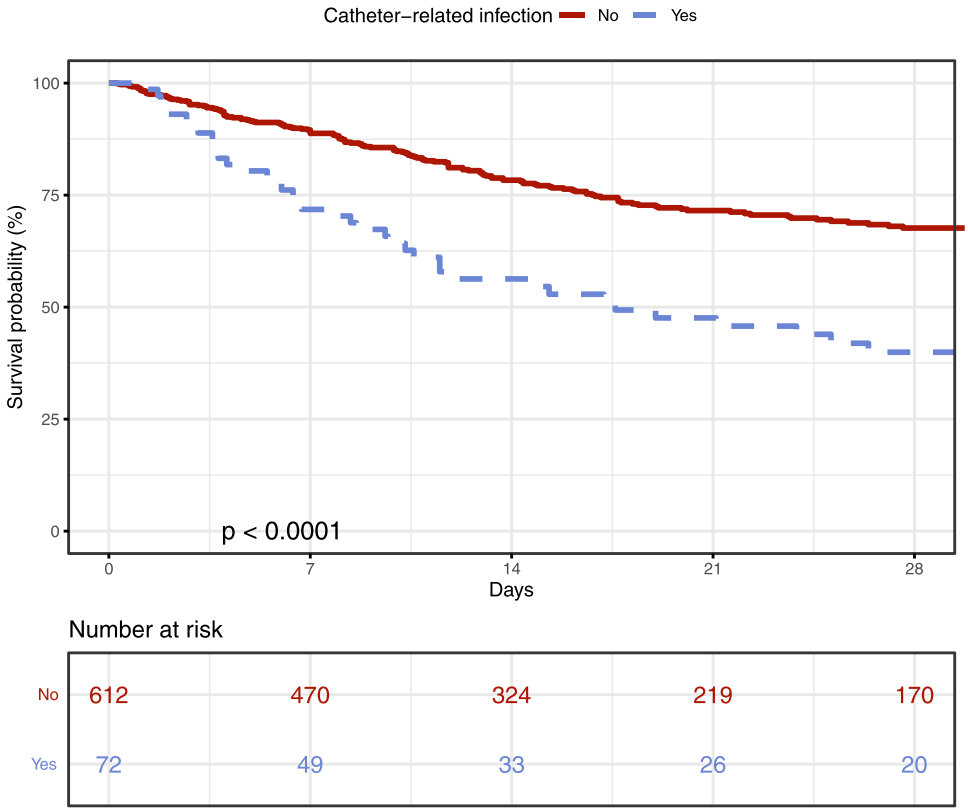


Fig. 2. **Survival curves stratified by suspected catheter-related infection**. Figure depicting survival curves stratified by suspected catheter-related infection with their respective 95% CI bounds. A log rank test showed a statistical significant difference ( $P < 0.0001$) between survival curves. Central venous catheters were right censored in case of hospital discharge or intensive care unit discharge, whichever was available.



critically ill COVID-19 patients is high, (2) prone ventilation for more than 5 days is associated with a greater risk for suspected catheter-related infection, and (3) in COVID-19 patients, a suspected catheter-related infection is associated with a higher mortality risk. We showed robustness of survival analysis in 2 sensitivity analyses, one which included one randomly selected CVC per patient and one that used a different definition for catheter-related infection.

Previous studies already showed a higher rate of bloodstream infections in COVID-19 ICU patients compared with ICU patients without COVID-19 (6,17,18). Ripa et al (19) observed that 9.3% of hospitalized COVID-19 patients experienced a secondary infection, of whom 85% had a bloodstream infection. Bardi et al (20) found that secondary infections were associated with higher mortality and longer ICU stay, and Pasquini et al (21) found a significantly higher mortality and bloodstream infection in hospitalized COVID-19 patients. Despite the heterogeneity of these studies, this indicates that bloodstream infections are common in COVID-19 ICU patients. Our results support this hypothesis. Consistent with previously mentioned literature, we found a 7.9% (suspected) catheter-related infection prevalence and incidence of 9.4 catheter-related infections per 1,000 catheter indwelling days. However, few studies also investigated risk factors and outcome of catheter-related infections in critically ill COVID-19 patients. Another potential reason for the high catheter-related infection rate might be the association with catheter-related thrombosis (22). Catheter-related thrombosis is more prevalent in COVID-19 patients due to a hypercoagulable state and subsequent macrovascular and microvascular thrombosis (23,24).

Prolonged prone ventilation, as our study shows, is a major risk factor for catheter-related infection. Several mechanisms may

Table 3. **Proportional hazards mortality**

| Covariates | n | Crude HR | 95% CI | Adjusted HR* | 95% CI |
|---|---|---|---|---|---|
| Suspected catheter-related infection | 684 | 2.50 | 1.69–3.40 | 1.78 | 1.25–2.53 |
| Age, per year increase | 684 | 1.05 | 1.02–1.08 | 1.05 | 1.02–1.08 |
| BMI, per kg/m$^2$ increase | 681 | 1.04 | 1.01–1.07 | 1.06 | 1.02–1.10 |
| Length of ICU stay, per day increase | 684 | 0.97 | 0.96–0.98 | 0.97 | 0.95–0.99 |
| Corticosteroid use | 684 | 0.89 | 0.61–1.29 | 1.05 | 0.71–1.54 |
| SOFA score, per point increase | 644 | 1.22 | 1.16–1.30 | 1.20 | 1.13–1.28 |

*A total of 642 CVCs were included in the multivariable analysis. Confidence intervals are robust confidence intervals taking multiple CVCs per patient into account.

BMI, body mass index; CI, confidence interval; CVC, central venous catheter; HR, hazard ratio; ICU, intensive care unit; SOFA, sequential organ failure assessment.

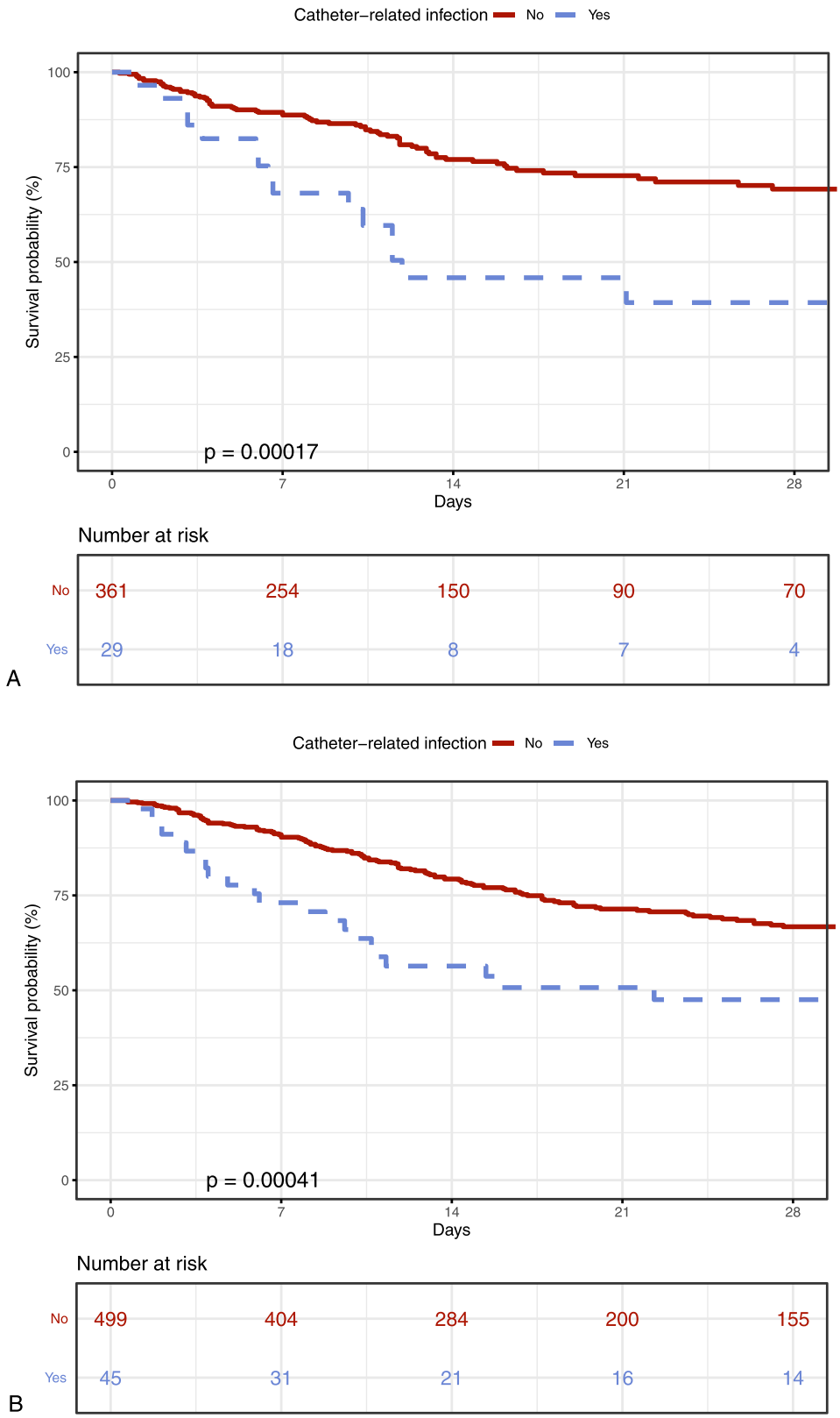


Fig. 3. **A, Survival curves stratified by suspected catheter-related infection: one randomly sampled central venous catheter per patient**. Figure depicting survival curves stratified by suspected catheter-related infection with their respective 95% CI bounds. Per every unique patient one central venous catheter was randomly sampled. A Log Rank test showed a statistical significant difference ( $P = 0.00017$) between survival curves. Central venous catheters were right censored in case of hospital discharge or intensive care unit discharge, whichever was available. **B, Survival curves stratified by suspected catheter-related infection: alternative definition.** Figure depicting suspected catheter-related infection incidence stratified by insertion site with their respective 95% CI bounds. An alternative infection definition was used: catheter-related infection was defined as a procalcitonin of at least 0.5 ng/mL at time of CVC removal and a CRP decrease of more than 50 mg/L within 5 days after CVC removal. A log rank test showed a statistical significant difference ( $P = 0.00041$) between survival curves. Central venous catheters were right censored in case of hospital discharge or intensive care unit discharge, whichever was available. CI, confidence interval; CRP, C-reactive protein; CVC, central venous catheter.

explain this observation. The process of turning patients can lead to friction at the insertion site, and because patients may lay prone for multiple days, difficulties with checking dressing integrity also increase the risk of catheter-related infection. Furthermore, inadvertent buildup of airway secretions and fecal material around insertion sites may develop. In contrast to previous studies, catheter-related infection rates did not differ between insertion sites. Femoral vein cannulation is reportedly associated with higher infection and thrombosis rates as compared with internal jugular and subclavian vein cannulation (5,25). However, according to national protocol in the Netherlands, all intubated ICU patients receive selective digestive decontamination (15), and most ICUs adhere to this protocol (26). Subsequently, this might mitigate the effect of insertion site on catheter-related infection rate because it potentially decreases the microbial bioburden at the femoral insertion site.

In non–COVID-19 critically ill patients catheter-related infections also have been associated with longer ICU length of stay and higher mortality (3). Nonetheless, it has been debated whether catheter-related infection is a marker rather than a cause of disease severity (27). The reported lower catheter-related infection rate, when infection control practices are strictly adhered, argues for a causal role (28). Because of shortages in personal protective equipment and the multitude of critically ill patients, infection control practices have been put under pressure during the COVID-19 pandemic. Intensive care unit staff was encouraged to group tasks and spare equipment, which might have reduced focus on infection control, for example, hand hygiene, and may have increased cross contamination (29).

A limitation of this study involves the definition for suspected catheter-related infection. Antibiotic administration around CVC removal was used as a surrogate measure, because microbiology data were not available in the DDW. This surrogate measure might have underestimated the real incidence of catheter-related infection, because, in case of relatively mild catheter-related infections, antibiotics might have been withheld, and which, on its turn, potentially explains the strong association of catheter-related infections with mortality in our study. Therefore, to check the robustness of our definition, we performed a sensitivity analysis in which an alternative definition for catheter-related infection was used. We showed this definition to be consistent with the primary one.

A major strength of the study is its size, which resulted in robust estimation of risks. Moreover, to our knowledge, there have not been any studies showing the association of prolonged prone ventilation with catheter-related infection. Another strength is the multicenter design; a full-admission electronic health record database was used that accounts for transfers between participating ICUs (9).

In our experience, prone ventilation complicates the maintenance of dressing integrity and examination of the insertion site. This study, therefore, serves as a reminder of the importance of infection control practices, especially during a challenging period such as the COVID-19 pandemic. Future studies should assess whether more focus on hygienic measures in prone-ventilated COVID-19 patients can prevent catheter-related infection.

In conclusion, this study shows that the prevalence and incidence of suspected catheter-related infection in critically ill COVID-19 patients is high, that prolonged prone ventilation is a risk factor for suspected catheter-related infection, and that suspected catheter-related infection is associated with a higher risk for mortality. Overall, we would like to emphasize the focus that should be put on hygienic measures, especially during prone ventilation, to prevent catheter-related infection in critically ill COVID-19 patients.

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