Association between Early Antibiotic Therapy and In-Hospital Mortality among Older Patients with SARS-CoV-2 Pneumonia

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ABSTRACT

Background: It is uncertain whether antibiotic therapy should be started in SARS CoV-2 pneumonia. We aimed to investigate the association between early antibiotic therapy and the risk of in-hospital mortality in older patients.

Methods: We performed a retrospective international cohort study (ANTIBIOVID) in five COVID-19 geriatric units in France and Switzerland. Among 1,357 consecutive patients aged 75 or more hospitalised and testing positive for SARS-CoV-2, 1072 had a radiologically confirmed pneumonia, of which 914 patients were still alive and hospitalized at 48 hours. To adjust for confounders, a propensity score for treatment was created, and stabilized inverse probability of treatment weighting (SIPTW) was applied. To assess the association between early antibiotic therapy and in-hospital 30-day mortality, SIPTW-adjusted Kaplan-Meier and Cox proportional hazards regression analyses were performed.

Results: Of the 914 patients with SARS-CoV-2 pneumonia, median age of 86, 428 (46.8%) received antibiotics in the first 48 hours after diagnosis. Among these patients, 147 (34.3%) died in hospital within one month vs 118 patients (24.3%) with no early antibiotic treatment. After SIPTW, early antibiotic treatment was not significantly associated with mortality (adjusted hazard ratio, 1.23; 95% CI, 0.92-1.63; *P* = .160). Microbiologically confirmed superinfections occurred rarely in both groups (bacterial pneumonia: 2.5% vs 1.5%, P = .220; blood stream infection: 8.2% vs 5.2%, P = .120; *Clostridioides difficile* colitis: 2.4% vs 1.0%, P = .222).

Conclusions: In a large multicentre cohort of older inpatients with SARS-CoV-2 pneumonia, early antibiotic treatment did not appear to be associated with an improved prognosis.

Keywords: COVID-19; superinfection; co-infection; bacterial; bacteraemia

INTRODUCTION

The COVID-19 pandemic is the most deadly outbreak worldwide since the Spanish influenza pandemic in 1918, and its burden has been particularly heavy in the older population. Nearly one third of older patients hospitalized with SARS-CoV2 pneumonia died in hospital (1–3). Most deaths are the result of respiratory failure linked to viral pneumonia, for which therapeutic management is still a matter of debate. However, the distinction between bacterial and viral pneumonia remains particularly difficult in practice, and influenza experience has shown that coinfections are not rare in viral pneumonia, especially in older individuals (4). Despite recent advances in this field (5), there is currently no distinctive tool to conclusively distinguish SARS-CoV-2 pneumonia from bacterial pneumonia. Because delayed antibiotic treatment has been associated with worse outcomes in bacterial pneumonia (6), empirical antibiotic treatment was initially recommended for COVID-19 pneumonia in many guidelines (7). Since then, increasing data have highlighted a very low frequency of documented bacterial co- or superinfection in COVID-19 (8–14). Moreover, the widespread use of empirical antibiotics during the current pandemic appears to have contributed to the development of multidrug-resistant microorganisms (15–17). Thus, the most recent guidelines consensually suggest a restrictive use of antibacterial drugs in patients with COVID-19 (10,18–20). However, the level of evidence for such recommendations remains very low and reposes on small-scale observational data (3,21–23). Interventional studies only focused on azithromycin and failed to demonstrate any benefit compared with usual care (24–26). Antibiotics remain still widely prescribed in practice (8,9,15), especially in frail older individuals (3,27).

To our knowledge, whether systemic antibiotic therapy should be prescribed in older patients with acute pneumonia and testing positive for COVID-19 has not yet been evaluated on a large scale. In a pilot study of older comorbid inpatients presenting with a SARS-CoV-2 pneumonia, we showed that one-month mortality did not differ whether patients received antibiotic treatment or not (3). We aimed to confirm this result in a larger multicenter cohort study.

METHODS

Data Source and Design

We performed a retrospective, multicenter cohort study using hospital records data from acute geriatric care units from four university hospitals and one regional hospital in France and Switzerland, during the first two waves of COVID-19 pandemic in Europe, from March 1, 2020, to December 31, 2020. Data were extracted from medical records in each hospital and anonymized before release to investigators.

This observational study was conducted in accordance with the Declaration of Helsinki and national standards. Geneva's committee for research ethics was consulted and approved the study. Each participant or his/her referee received an information letter and was invited to express his/her opposition to participation in the study.

Patients

We included all consecutive patients aged 75 years or older presenting with acute, radiologically-confirmed pneumonia and testing positive for SARS-CoV-2 with real-time polymerase chain reaction (RT-PCR). Acute pneumonia was defined according to the American guidelines (28), in the acute presence of 2 or more of the following signs: new cough, sputum production, dyspnea, pleuritic pain, abnormal temperature (<35.6°C or >37.8°C), or altered breathing sounds on auscultation, and a new infiltrate on chest imaging.

We excluded patients who were discharged or died within 48 hours after admission or for whom a bacterial co-infection requiring antibiotics was documented at admission (i.e. positive culture results in the presence of suggestive clinical features).

Based on our previous studies (36% in-hospital mortality rate, 2/1 exposed/non exposed ratio) (2,3) and considering a 0.7 relative hazard as clinically significant, a total sample size of 847 patients was estimated to provide 80% power, using a 2-tailed hypothesis at an α level of .05.

Exposure and Primary Outcome Measure

We compared patients who received early systemic antibiotic treatment, i.e. within the first 48 hours after diagnosis, with those who did not receive any antibiotic in these first 48 hours. The primary outcome was in-hospital 30-day mortality.

Data collection and management

We recorded the following characteristics as potential confounders at admission:

Hospital centre, age, sex, underlying diseases and Charlson comorbidity index (29), clinical presentation (delay between symptom onset and positive RT-PCR test, heart rate, systolic and diastolic blood pressure, temperature, oxygen saturation, oxygen flow, respiratory rate, confusion) biological parameters (leucocyte count, C-reactive protein, albumin, urea, creatinine), prognosis scores (WHO severity class (18), CURB65 (30), Pneumonia severity index (31), NEWS2 (32), quickSOFA (33)). Place of acquisition of pneumonia was also recorded: community-acquired pneumonia (CAP), nursing-home-acquired pneumonia (NHAP) and late-onset hospital-acquired pneumonia (HAP), defined as symptom onset occurring after 4 days of hospitalization (34).

In-hospital management, including acute treatments (corticosteroid therapy with a daily dose ≥ 6mg of dexamethasone or equivalent (35), tocilizumab, remdesivir, lopinavir/ritonavir, chloroquine), antibiotic treatment (class: cephalosporins, penicillin with betalactamase inhibitors, macrolides, fluoroquinolones, and duration of first-line treatment) and palliative treatment (morphine,

midazolam), as well as superinfections occurring during hospital stay (suspected bacterial pneumonia and microbiologically confirmed pneumonia, bloodstream infection, urinary tract infections and *Clostridioides difficile* colitis) were reported. Confirmed superinfection was defined as any infection with clinical features and a positive microbiological sampling (blood cultures, sputum or aspiration cultures or positive serology for *Chlamydia pneumoniae*, urine cultures, positive enzyme immunoassay or PCR for *C. difficile* toxin). Suspected bacterial pneumonia was defined as a clinical suspicion of superinfection leading to an antibiotic prescription during hospital stay.

Vital status at discharge, hospital length of stay, transfer to intensive care unit, and palliative care requirement were also recorded.

To avoid excluding patients with missing values for several of the potential confounders, multiple imputation was used to handle missing data (< 10% for all covariates) that were assumed to be missing at random for all covariates. Missing values were imputed 10 times, by sampling from their posterior predictive distribution, conditional on the observed data. In all subsequent analyses, Rubin's rules were applied to summarize the effect estimates and variances from the 10 different analyses across multiple imputed data sets (36).

Statistical Analysis

Continuous variables were described using medians and interquartile ranges, and categorical variables were described using frequencies and percentages. Wilcoxon rank sum, $\chi 2$, and log-rank tests were used to evaluate the statistical significance of unadjusted continuous, categorical, and time-to-event data, respectively. All tests were 2-tailed, and a *P* value of less than .05 was considered statistically significant. Statistical analyses were performed using SPSS 21.0 (IBM Corp, Armonk, NY) and R 4.0.4 software (R Foundation for Statistical Computing, Vienna, Austria).

Propensity Model

Older patients who receive antibiotic treatment often have a more severe presentation than those who do not. To account for potential confounding in the association of antibiotic use and mortality, we created a propensity score for each patient and applied inverse probability weighting. The propensity score represented the predicted probability of receiving antibiotic treatment and was determined using a logistic regression model with 48-hour antibiotic use as the dependent variable and the aforementioned potential confounders at admission (listed in table 1) as the independent variables. Each patient's propensity score was then used to create an inverse probability weight for that patient. Stabilized inverse probability of treatment weight (SIPTW) was then obtained by multiplying the inverse probability weight by the marginal probability of receiving the actual treatment received (i.e. early antibiotic treatment or not) (37). After adjusting for these weights, a propensity-weighted sample was thus created that was more balanced with respect to potential confounders included in the regression model.

Before assessing the outcome, we confirmed that the weighted sample was balanced using the following parameters: standardized difference, -0.15 to 0.15; and variance ratio, 0.5 to 2.0 (38). We examined overlap plots of the propensity scores by treatment group to ensure that the area of common support was adequate.

Outcomes

SIPTW-adjusted Kaplan-Meier curves were calculated to compare overall in-hospital 30-day survival between patients who received early antibiotic treatment and those who did not. We further fitted an SIPTW-adjusted Cox proportional hazards regression model to compute the corresponding hazard ratio (HR). To avoid informative censoring, patients discharged from hospital were regarded as surviving to 30 days.

RESULTS

Demographics and Characteristics

From March 1, 2020, to December 31, 2020, 1369 consecutive patients over 75 years of age and positive for SARS-CoV2 (RT-PCR) were hospitalized. Among them, 297 had no pneumonia at admission, 54 had microbiologically documented bacterial infection at admission (33 bloodstream infection, 21 bacterial pneumonia), 100 died or were discharged in the first 48 hours, and 4 refused to participate. Finally, 914 patients were eligible for analysis (Figure 1). The median age was 86 [81-90] years, and 448 patients (49.0%) were male.

A total of 428 patients (46.8%) received antibiotic treatment in the first 48 hours. There was wide variability in early antibiotic prescription rate among the 5 centers, ranging from 11.2% to 74.9%. Patient characteristics at admission are presented in Table 1. Age did not significantly differ between patients receiving early antibiotic treatment or not. Patients who received initial antibiotic treatment were more likely to be male (53.5% vs 45.1%, $P = .011$) and to have community-acquired pneumonia (68.5% vs 48.1%, $P < .001$) rather than nursing-home (17.8% vs 23.0%, $P = .048$) or hospital-acquired pneumonia (14.1% vs 27.4%, $P < .001$). Underlying diseases were equally frequent in both groups (Charlson Comorbidity index: 3 [2-5] vs 3 [1-5], $P = .473$), but of different distribution: among patients under early antibiotic treatment, chronic heart failure (25.4% vs 32.5, $P = .019$) and cognitive disorders (35.9% vs 42.7%, $P = .037$) were less frequent, whereas chronic kidney disease (43.4% vs 30.7%, $P < .001$) was more frequent.

Clinical presentation

Diagnosis of SARS-CoV-2 pneumonia was confirmed by a positive RT-PCR test within a median of 3 days [1-7] after symptom onset in both groups (Table 1). Clinical presentation at admission differed in the two groups, with a more severe presentation among patients with early antibiotic treatment: heart

rate (86 [76-98] vs 81 [76-98] beats per minute, $P < .001$), respiratory rate (24 [20-29] vs 22 [20-26] breaths per minute, $P < .001$) and temperature (37.8 [36.9-38.5] vs 37 [36.4-38]°C, $P < .001$) were significantly more elevated.

Patients with early antibiotic treatment had a higher leucocyte count (6.90 [5.05-9.94] vs 6.39 [4.80-8.70] G/L, $P = .004$) and C-reactive protein level (85 [38-140] vs 50 [21-98], $P < .001$).

Severity score

The WHO severity scale, specifically developed to stratify COVID-19 risk (18), was more elevated in patients with early antibiotic treatment (S3: severe pneumonia for 51.6 vs 45.7% of patients, $P < .001$), as was the NEWS2 score (32) (6 [4-8] vs 5 [3-7] , $P < .001$). Other prognostic tools in pneumonia (PSI (31), CURB65 (30)) and in sepsis (qSOFA (33)) did not significantly differ between the two groups (Table 1).

After SIPTW, the differences in the baseline covariates that were apparent in the overall sample were no longer present (Table 1 and eFigure in the Supplement).

Treatments in Hospital

The acute treatments used for SARS-CoV-2 pneumonia during the hospital stay are presented in Table 2. After SIPTW, they did not significantly differ between the two groups, except for antibiotics. Corticosteroids (daily dose ≥ 6mg of dexamethasone or equivalent) were as frequently prescribed in patients with or without early antibiotic treatment (38.8% vs 39.6%, $P = .825$), as were palliative treatments (morphine: 37.4% vs 34.8%, $P = .825$; midazolam: 22.7% vs 24.4%, $P = .601$).

Median duration of first line of antibiotics was 6 [5-8] days in the early treatment group. Two thirds of the patients without early antibiotic treatment received antibiotics later during their hospital stay.

Beta-lactams were the most frequent antibiotic prescriptions in both groups (cephalosporins 54.1% vs 38.8%, penicillins + betalactamase inhibitors 54.0% vs 39.5%, *P* < .001) followed by macrolides (26.0% vs 23.1%, *P* = .335) and fluoroquinolones (5.1% vs 2.5%, *P* = .047).

Co-infections

In the SIPTW cohort, suspected bacterial pneumonia was twice as frequent during the hospital stay in patients with early antibiotic treatment (37.6% vs 20.3%, *P* < .001). However, documented superinfections were rare in both groups (documented bacterial pneumonia: 2.5% vs 1.5%, *P* = .220; documented bloodstream infection: 8.2% vs 5.2%, *P* = .120). *C. difficile* colitis infections were also rare in both groups (2.4% vs 1.0%, *P* = .222).

Microbiological data are presented in Table 3 (unweighted cohort). Pneumococcal (3 patients) and staphylococcal (*Staphylococcus aureus*: 4 patients) superinfections were rare. Gram negative bacilli were the majority, both in bloodstream infections (*Escherichia coli*: 25 patients, *Pseudomonas aeruginosa*: 6 patients, other gram negative bacilli: 8 patients) and in documented bacterial pneumonia (*P. aeruginosa*: 4 patients, other gram negative bacilli: 5 patients). Bacterial superinfections occurred earlier in patients receiving early antibiotic treatment (1 [0-6] vs 8 [6-13] days for bloodstream infection, 6 [4-8] vs 2 [0-5] days for documented bacterial pneumonia, *P* = < .001)

Outcomes

SIPTW-adjusted HR for in-hospital 30-day mortality in patients with versus without early antibiotic treatment was 1.23 [0.92-1.63] (*P* = .160). SIPTW-adjusted Kaplan-Meier curves are presented in Figure 2: in-hospital 30-day mortality did not significantly differ between the two groups (log-rank test, *P* = .190).

After SIPTW, hospital stays were as long in patients with early antibiotic treatment as in those without (11 [7-18] vs 11 [6-20], *P* = .988). The in-hospital 30-day mortality rate did not significantly differ in the two groups (32.0% vs 27.7%, *P* = .155). Despite the high mortality rate, transfer to intensive care unit was rare (5.7% vs 6.5%, *P* = .524) and patients often received palliative care (24.5% vs 19.4%, *P* = .099).

DISCUSSION

Antibiotics are undoubtedly one of the most important advances in medicine, even though the inappropriate use of these drugs threatens their effectiveness. There has been considerable concern about the widespread use of antibiotics since the beginning of the COVID-19 pandemic. Many authors have detected an increase in highly resistant pathogens and plead for raised antimicrobial stewardship efforts (14–17). However, the clinical presentation of severe COVID-19 is frequently indistinguishable from bacterial or fungal sepsis. Given the paucity of active therapeutics, physicians are often tempted to prescribe antibiotics in frail older patients with a severe presentation. Thus, there is a need for a higher level of evidence to support recent guidelines (10,18–20) against systematic antibiotic treatment in SARS-CoV-2 pneumonia, especially in the geriatric setting.

Few interventional studies have assessed the usefulness of antibiotic treatment in COVID-19. All trials comparing azithromycin to usual care failed to demonstrate any benefit of this antibiotic treatment (24–26). To the best of our knowledge, there is to date no interventional data concerning other antibiotic treatments. In particular, recommended empirical antibiotics for acute pneumonia (34,39), which are widely used in SARS-CoV-2 pneumonia (9), have not been evaluated in interventional studies nor in large observational studies.

The main results of this large multicenter cohort are as follows: 1) the in-hospital mortality rate for older patients hospitalized with SARS-CoV-2 pneumonia was nearly 30% at 30 days; 2) half of patients received early antibiotic treatment at admission; 3) bacterial superinfection during hospital

stay was seldom documented in patients with or without early antibiotic therapy; and 4) early antibiotic treatment was not associated with a better in-hospital prognosis.

Our results are consistent with the literature, highlighting that more than 70% of patients with SARS-CoV-2 infection receive antibiotics, but less than 10% experience bacterial and fungal coinfection (8,11,12). However, antibiotic use varies considerably from one center to another (8,9,40), as highlighted in our study (from 11.2% to 74.9% of patients), stressing the need for stronger evidence on this issue. Broad-spectrum therapies, mainly beta-lactams, were frequently prescribed, as recommended in recent guidelines for bacterial pneumonia (34,39). Contrary to other reports (9,11), macrolides were a minority of antibiotic prescriptions. As in other reports, we found that the likelihood of early antibiotic prescription was correlated with the initial severity of pneumonia, rather than with comorbidities (21). In this elderly population, age was no longer a criterion for early antibiotic prescription.

Here, one interesting result is the relatively high frequency of bloodstream infections compared with previous reports in younger patients (12,41), although they may have been slightly overestimated by blood culture contaminations (DNAse negative *staphylococci*) (41). Our study population was expected to be at higher risk for severe superinfections for several reasons. First, older patients have already shown to be more prompt to develop superinfections during COVID-19 (42). Second, COVID-19 could particularly predispose to bacterial infection since bacteremia was found to be more frequent in COVID-19 than non-COVID-19 critically ill patients (43). This risk may be higher than in other infections: patients with COVID-19 were 2.5 times more likely to develop bacteremia than patients with influenza (44). The reasons for such a high frequency are not elucidated. However, the high frequency of *Enterobacteriaceae*, *Enterococci* and *Candida*, already documented by others in COVID-19 (9,11,14,45,46), suggest a potential digestive translocation (47), as already described at the acute phase of bacterial pneumonia (48). Digestive involvement is frequent in COVID-19 patients, especially in the older population (49), and could be due to ischemic damage in the gastrointestinal tract rather than direct viral damage (47). Interestingly, *C. difficile* colitis was rare, as also already reported by others. Even if antibiotic treatment remains a major risk factor for *C. difficile* infection in

COVID-19 inpatients (50), this low rate could be due to COVID-19-linked reinforced cleaning procedures and reduced patient mobility (51).

Whether systematic early antibiotic treatment should be introduced in the early phase of SARS-CoV2 pneumonia remains a current issue. In a recent single-center study, authors showed that early administered antibiotics did not impact mortality in critically ill patients with COVID-19 (22), confirming similar results in non-critically ill units (3,21). However these previous results did not have sufficient power to adequately assess this question. We believe that our large multicenter data further reinforce previous findings and strongly discourage systematic antibiotic treatment. Further research is needed to define the patients for whom antibiotics should be indicated and in which settings. Our results also show that documented bacterial superinfections often develop a week or more after COVID-19 diagnosis (median of 8 days) in patients without early antibiotic treatment, further mitigating the benefit of a systematic strategy. Some authors suggest that antibiotic therapy should be reserved for the patients with the most severe presentations (10,52), but no data to date support this position. Biomarkers (C-reactive protein, procalcitonin) may play a role in deciding when antibiotics can be withheld (5,46). Also, the ability of thoracic computed tomography to distinguish alveolar infiltrates associated with bacterial pneumonia as opposed to the typical glass ground opacities seen in COVID-19 remains to be evaluated (10).

This study has some limitations. First, only patients with COVID-19 hospitalized in a medical ward were included, and those initially hospitalized in the ICU were not considered. These results cannot be extrapolated to more severe patients, especially those under mechanical ventilation. Second, because no systematic sampling procedure was performed in these wards (screening was based on clinical judgment), microbiological documentation was often missing in this retrospective study. Thus, we probably underestimated bacterial infection occurrence. However, we believe that this study represents the real-world situation in most hospitals. Third, most of patients in the group without early antibiotic treatment during the first 48 hours did receive antibiotics later during their hospital stay.

This could have potentially mitigated any antibiotic benefit effect in the early treatment group. Again, this situation was expected in a very elderly hospital population with comorbidities. However, patients without any antibiotic treatment during hospital stay had a crude lower mortality rate (19.5%) than patients with early (34.4%) and delayed antibiotic treatment (28.0%), suggesting no benefit of such treatment. Fourth, even with an adjustment on comorbidities and clinical parameters at admission, including usual prognostic criteria in COVID-19, the results could be biased by unmeasured confounding due to factors such as frailty, which might not be well captured in routinely collected data. This study remains observational and only a randomized clinical trial could support a definite statement.

In this large multicenter study, half of older patients hospitalized with SARS-CoV-2 pneumonia received early antibiotic treatment after diagnosis even though no bacterial co-infection was documented. The likelihood of early antibiotic prescription was correlated with pneumonia severity rather than comorbidities. After adjustment for confounders, early antibiotic treatment was not associated with a decrease in in-hospital mortality or with superinfection occurrence. According to these data, antibiotic therapy should not be prescribed systematically for older patients with SARS-CoV2. Further investigations are required to target patients most at risk of bacterial superinfection, and interventional studies are needed to confirm these observational findings.

Funding: None declared.

Conflict of interests

All authors declare no competing interests.

Acknowledgments: We thank Sylvia Rostoix, Michèle Vourc'h, Sylvie Leconte for the data collection and Suzanne Rankin for the English review of the manuscript. They were not compensated for their contributions.

Author Contributions: Alain Putot and Stéphane Sanchez had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Alain Putot, Virginie Prendki

Acquisition, analysis, or interpretation of data: Alain Putot

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Alain Putot, Arthur Hacquin

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Data sharing

The study protocol and the individual, de-identified patient data that underlie the results reported in this Article (text, tables, figures) are available on reasonable request from the corresponding author (AP; alain.putot@chu-dijon.fr) under certain conditions (with the consent of all participating centres and with a signed data access agreement).

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Table 1: Characteristics of Patients at Admission (n (%) or Median [interquartile range])

	Unweighted Study Population[a]				Weighted Study Population[a]		
	Antibiotics N = 428	**No Antibiotics N = 486**	***P***	**Standardized Difference**	**Antibiotics**	**No Antibiotics**	**Standardized Difference**
Hospital Centre							
Centre (1)	135 (31.5)	126 (25.9)	<.001	.124	29.8	28.7	.024
Centre (2)	63 (14.7)	110 (22.6)		-.205	20.9	19.3	.040
Centre (3)	82 (19.2)	94 (19.3)		-.003	19.7	20.0	-.008
Centre (4)	14 (3.3)	111 (22.8)		-.619	9.3	13.6	-.135
Centre (5)	134 (31.3)	45 (9.3)		.561	20.3	18.4	.048
Demographics							
Age (years)	85.7 [80.9-90.6]	86.2 [81.5-90.2]	.655	-.039	86.2 [81.4-90.8]	86.1 [81.3-90.1]	.035
Male	229 (53.5)	219 (45.1)	.011	.169	51.1	48.9	.044
Community-acquired pneumonia	292 (68.2)	241 (49.6)	< .001	.422	59.5	56.6	.059
Nursing-home-acquired pneumonia	76 (17.8)	112 (23)		-.129	22.6	22.8	-.005
Hospital-acquired pneumonia	60 (14)	133 (27.4)		-.330	17.8	19.9	-.054
Severity scores							

Pneumonia Severity Index	120 [104-136]	121 [103-143]	.536	-.156	120 [105-136]	120 [101-141]	.035
CURB65 >2	192 (44.9)	208 (42.8)	.531	.328	45.1	45.3	-.004
NEWS2	6 [4-8]	5 [3-7]	<.001	.373	6 [4-8]	5 [4-7]	.070
qSOFA >1	73 (17.1)	82 (16.9)	.941	.005	18.2	17.4	.021
WHO score S2	150 (35.0)	200 (41.1)	<.001	-.365	33.8	36.5	-.012
WHO score S3	221 (51.6)	222 (45.7)		.118	52.1	49.6	.050
WHO score S4	57 (13.3)	64 (13.2)		.003	14.1	13.9	.006
Underlying disease							
Chronic heart failure	107 (25.4)	153 (32.5)	.019	-.157	28.2	30.2	-.044
Chronic respiratory disease	62 (18.1)	82 (20.8)	.360	-.068	20.7	21.6	-.022
Chronic kidney disease	183 (43.4)	147 (30.7)	< .001	.266	36.7	35.8	.019
Chronic liver disease	18 (4.2)	26 (5.4)	.411	-.056	3.9	5.0	-.053
Cognitive disorders	152 (35.9)	206 (42.7)	.037	-.139	39.5	39.9	-.008
Stroke	85 (20.2)	90 (18.8)	.607	.035	20.1	19.5	.015
Myocardial Infarction	68 (15.9)	80 (16.5)	.804	-.016	15.6	16.5	-.025
Active Neoplasia	67 (15.8)	82 (17.1)	.595	-.035	16.9	16.7	.005

Diabetes	104 (24.6)	130 (27)	.403	-.055	24.7	24.6	.002
PAD	45 (10.6)	80 (16.7)	.009	-.179	14.0	14.8	-.023
Charlson Comorbidity index	3 [2-5]	3 [1-5]	.473	.063	3 [2-5]	3 [1-4]	.016
Clinical presentation							
Delay symptoms – diagnosis* (days)	3 [1-7]	3 [1-7]	.541	-.084	2 [1-6]	2 [1-7]	-.016
Heart rate (/min)	86 [76-98]	81 [71-94]	< .001	.258	85 [75-97]	84 [73-96]	.005
SBP (mmHg)	131 [117-144]	133 [120-149]	.086	-.100	131 [118-146]	132 [119-148]	-.003
DBP (mmHg)	70 [62-78]	71 [63-81]	.091	-.058	70 [62-79]	71 [63-80]	-.003
Temperature (°C)	37.8 [36.9-38.5]	37 [36.4-38]	< .001	.083	37.6 [36.8-38.3]	37.2 [36.6-38]	.027
O_2 Saturation (%)	94 [92-96]	94 [92-96]	.057	-.099	94 [92-96]	94 [92-96]	.005
Oxygenation (L/min)	0.5 [0-2]	0 [0-2]	.301	.042	1[0-2]	1 [0-2]	.014
Respiratory rate (/min)	24 [20-29]	22 [20-26]	< .001	.793	25 [22-28]	25 [21-28]	.007
Confusion	72 (16.8)	102 (23.9)	.109	-.176	20.6	20.7	-.002
Biology							
Leucocytes (G/L)	6.90 [5.05-9.94]	6.39 [4.80-8.70]	.004	.163	7.39 [5.10-9.20]	7.00 [5.19-9.20]	.027
Neutrophils (G/L)	5.29 [3.68-7.77]	4.60 [3.27-6.93]	.003	.215	6.10 [3.84-7.02]	5.40 [3.52-6.79]	.022

Lymphocytes (G/L)	0.85 [0.57-1.27]	0.93 [0.63-1.25]	.180	-.036	1.02 [0.61-1.83]	0.97 [0.64-1.53]	.035
Platelets (G/mL)	191 [153-261]	204 [152-279]	.150	-.120	203 [156-253]	205 [149-265]	-.036
C-reactive protein (mg/L)	85 [38-140]	50 [21-98]	<.001	.398	83 [38-116]	70 [26-117]	.069
Albumin (g/L)	31 [27-36]	32 [28-36]	.211	.120	31 [29-34]	32 [29-35]	-.060
Urea (mmol/L)	9.0 [6.4-13.1]	8.5 [6-13.3]	.352	.086	9.3 [6.8-11.9]	9.0 [6.4-13.1]	.023
Creatinine (umol/L)	91 [74-128]	89 [67-119]	.049	.007	97 [75-120]	94 [69-120]	.011

DBP; Diastolic blood pressure; PAD: peripheral artery disease; SBP :systolic blood pressure; WHO: World Health Organisation

[a]Data are presented as number (percentage) of patients unless otherwise indicated.

[b]Data are presented as percentage of patients unless otherwise indicated.

*delay between symptom onset and positive SARS-CoV2 Real-Time Polymerase Chain Reaction.

Table 2: In-hospital Management and Outcomes (n (%) or Median [interquartile range])

	Unweighted Study Population[a]			Weighted Study Population[b]		
	Antibiotics N = 428	**No Antibiotics N = 486**	***P***	**Antibiotics**	**No Antibiotics**	***P***
Therapeutics						
Corticosteroids*	141 (32.9)	198 (40.7)	.015	38.8	39.6	.825
Tocilizumab	46 (10.7)	25 (9.3)	.453	9.2	9.9	.513
Remdesivir	46 (10.7)	37 (7.6)	.100	8.3	9.1	.657
Lopinavir/ritonavir	71 (16.6)	39 (8.0)	<.001	13.1	9.3	.070
Chloroquine	65 (15.2)	56 (11.5)	.103	12.3	13.7	.560
Morphine	144 (33.6)	157 (32.3)	.667	37.4	34.8	.420
Midazolam	82 (23.7)	77 (19.6)	.181	24.4	22.7	.601
Antibiotic treatment						
All antibiotics	428 (100)	297 (61.1)	<.001	100	66.1	<.001
Cephalosporin	265 (61.9)	135 (29.9)	<.001	54.1	38.8	<.001
Penicillin + inhibitor	201 (47.0)	185 (41.0)	.076	54.0	39.5	<.001
Macrolide	136 (31.8)	78 (17.3)	<.001	26.0	23.1	.335
Fluoroquinolone	26 (6.1)	11 (2.4)	.007	5.1	2.5	.047
First line of treatment length (days)	6 [5-8]	1 [0-5]	<.001	6 [5-8]	2 [0-6]	<.001
Co-infections						
Suspected bacterial pneumonia	147 (34.3)	103 (21.2)	<.001	37.6	20.3	<.001
Documented bacterial pneumonia	10 (2.3)	6 (1.2)	.205	2.5	1.5	.220
Blood stream infection	44 (11)	18 (3.7)	<.001	8.2	5.2	.120
Urinary tract infection	36 (8.4)	38 (7.8)	.597	8.7	7.9	.579
C. difficile infection	6 (1.4)	7 (1.4)	.961	2.4	1.0	.222
Outcomes						

Length of hospital stay (days)	10 [7-17]	12 [7-20]	.037	11 [7-18]	11 [6-20]	.988
Transfer to intensive care unit	23 (4.5)	29 (6.7)	.399	5.7	6.5	.524
Palliative care requirement	72 (20.8)	63 (16.1)	.097	24.5	19.4	.099
30-day in-hospital death	147 (34.3)	118 (24.3)	.001	32.0	27.7	.155

[a]Data are presented as number (percentage) of patients unless otherwise indicated.

[b]Data are presented as percentage of patients unless otherwise indicated.

*Equivalent ≥ 6mg dexamethasone

Table 3: Microbiological Documentation of In-hospital Superinfections (n or Median [Interquartile Range])

	Antibiotics N = 428	**No Antibiotics N = 486**
Blood stream infection	44	18
Delay# (days)	1 [0-6]	8 [6-13]
Escherichia Coli	18	7
Pseudomonas aeruginosa	4	2
Other gram negative bacilli*	5	3
Enterococcus spp.	3	2
Streptococcus spp.	4	0
Staphylococcus aureus	3	1
Other staphylococcus	8	4
Candida spp.	1	1
Pneumonia	10	6
Delay# (days)	2 [0-5]	6 [4-8]
Streptococcus pneumoniae	2	1
Pseudomonas aeruginosa	2	2
Serratia marcescens	0	1
Stenotrophomonas maltophilia	2	0
Enterobacter cloacae	1	0
Citrobacter freundii	1	0
Chlamydia pneumoniae	2	2

* *Klebsiella pneumoniae (3), Klebsiella aerogenes, Proteus mirabilis, Serratia marcescens, Acinetobacter baumanii, Actinotignum shaali*

delay between first positive SARS CoV2 real time polymerase chain reaction and positive bacterial sampling

Table titles and figure captions

Table 1: Characteristics of Patients at Admission (n(%) or median [interquartile range])

Table 2: In-hospital Management and Outcomes (n (%) or Median [interquartile range])

Table 3: Microbiological Documentation of In-hospital Superinfections (n or Median [Interquartile Range])

Figure 1:

Diagram of Patient Eligibility and Flow

Figure 2:

Propensity Score-Weighted 30-Day In-hospital Survival Curve for Older Patients Who Received Antibiotics versus No Antibiotics within the First 48 Hours of the Diagnosis of SARS-COV-2 Pneumonia

Figure 1

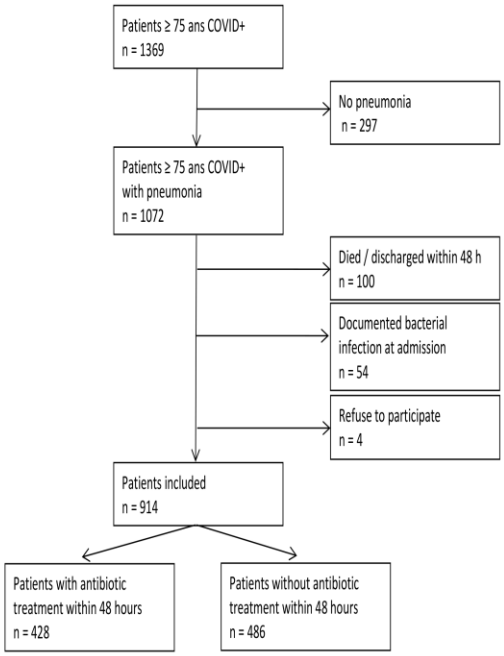

Figure 2