Pneumonia

BRIEF REPORT

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# Outcomes of corticosteroid therapy in patients with viral community-acquired pneumonia

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## Abstract

**Aim** The objective of this study was to assess the therapeutic effects of corticosteroids in adult patients hospitalized with viral community-acquired pneumonia.

**Methods** This is a retrospective analysis of data collected prospectively from November 1996 to June 2024. All adult patients with viral community-acquired pneumonia were enrolled. The primary outcome was 30-day mortality. Secondary outcomes included all-cause in-hospital mortality, ICU admission, length of ICU and hospital stay, mechanical ventilation, and 1-year mortality. Propensity score matching (PSM) was used to obtain balance among the baseline variables in the two groups.

**Results** Of the 524 patients with viral pneumonia, 30 (6%) received corticosteroids and 494 (94%) did not. Patients were primarily male ($n=299$, 57%), with a median [Q1-Q3] age of 66.9 [55–81] years. The 3:1 propensity matching procedure identified 90 patients not treated with corticosteroid (CS-) as controls. After PSM, no difference in 30-day mortality was found [7% (95%CI 1 to 22%) vs. 4% (95%CI 1 to 11%), $p=0.639$]. The risk of death at 30 days did not differ significantly in unmatched and matched cohorts [Hazard Ratio (HR) 1.33 (0.32–5.63), $p=0.695$ vs. HR 1.51 (0.28–8.27), $p=0.632$, respectively]. Nor were differences found in hospital length of stay, ICU admission and length of stay, or mechanical ventilation requirement and duration between matched and unmatched CS + and CS-.

**Conclusions** There were no significant differences in the primary and secondary outcomes regarding the use of corticosteroids in patients with viral pneumonia.

**Keywords** Virus, Viral pneumonia, Corticosteroids, Community-acquired pneumonia

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## Introduction

The COVID-19 pandemic highlighted the serious threat posed by respiratory viruses for global health [1, 2]. Viral pneumonia can be associated with complications such as sepsis or cardiovascular events [3], especially in the most vulnerable populations such as elderly patients, patients with multiple comorbidities, and the immunocompromised [4–7]. Early diagnosis and antiviral and adjunctive therapy are associated with improved outcomes in patients with viral CAP [3]. However, several systematic reviews and meta-analyses have provided strong scientific evidence of a relationship between the use of corticosteroids and higher rates of mortality in patients with severe influenza infection [8, 9]. Current ATS/IDSA guidelines [10] advise against routine use of corticosteroids in adults with severe influenza pneumonia. This study assessed the therapeutic effects of corticosteroids in patients affected by viral CAP.

## Methods

This is a retrospective observational cohort study of all consecutive adult patients with viral CAP admitted to the hospital between November 1996 and June 2024. Data were collected prospectively. CAP was defined as a new infiltrate on chest radiography and clinical signs/symptoms suggestive of lower respiratory tract infection. Viral etiology was considered definitive if at least one of the following criteria was fulfilled: (1) a four-fold increase in the IgG titer for respiratory viruses; (2) virus isolation in cell cultures; (3) detection of respiratory viruses by reverse-transcriptase (RT-PCR) assays; (4) detection of antigens by IFA. Polymicrobial pneumonia was defined as pneumonia due to more than one pathogen. Patients were divided into a corticosteroid group (CS+) and a non-corticosteroid group (CS-) according to whether they were treated with glucocorticosteroids during hospitalization; the decision to treat patients with corticosteroids was made by the attending physician. The primary outcome was 30-day mortality, while secondary outcomes included all-cause in-hospital mortality, ICU admission, length of ICU and hospital stay, mechanical ventilation, and 1-year mortality. Our hospital's institutional review board approved the study: Register2009/5451).

### Statistical analysis

Descriptive statistics were used to assess the basic features of the study data. Categorical variables were compared using the chi-squared test or Fisher's exact test, while continuous variables were compared using the non-parametric Mann-Whitney U test. The propensity score matching (PSM) method [11, 12] was used to obtain the balance among baseline variables between patients with and without systemic corticosteroids. To match the two cohorts, we used a 1:3 nearest-neighbor matching with age, sex, chronic respiratory disease, chronic cardiovascular disease, diabetes mellitus, neurologic disease, chronic renal disease, chronic liver disease, previous neoplasm, previous inhaled corticosteroid therapy, influenza vaccine, PSI score, SOFA score, C-reactive protein, neutrophils, lymphocytes, $PaO_2/FiO_2$, septic shock, and year of admission as covariates, without replacement and with a caliper width of 1. The association between systemic corticosteroids and mortality (in-hospital, 30-day, and 1-year) was analysed by means of Cox regression analyses according to the etiology group (only respiratory virus and bacterial plus respiratory virus). Survival curves of patients with and without systemic corticosteroids were obtained using the Kaplan-Meier method and compared using the Gehan-Breslow-Wilcoxon test [13]. In addition, modification of effect by factors potentially associated with patient outcomes and systemic corticosteroid use was assessed by an interaction term, and outcomes were then examined according to etiology group.

## Results

During the study period, 7333 patients were admitted to our hospital for CAP. After exclusions, 524 patients with viral pneumonia were included in the study, 30 of whom (6%) received corticosteroids, and 494 (94%) did not. See supplementary Fig. 1. Patients were primarily male ($n=299$, 57%), with a median [Q1-Q3] age of 66.9 [55–81] years old. One hundred and eighty-five (35%) patients had a PSI risk class IV - V, 112 (21%) were classified as severe CAP, 23 (4%) suffered from septic shock at hospital admission, and 25 (5%) presented ARDS. Co-infection by both virus and bacteria was present in 152 (29%) patients, with influenza virus plus *S. pneumoniae* being the most frequent co-infection (54 [10%]). Respiratory viruses are shown in Supplementary Table 1. Thirty (6%) patients received corticosteroid (CS+) therapy during their hospital stay. In-hospital, 30-day, and 1 year- mortality rates were 32 (6%), 25 (5%), and 40 (8%) respectively. CS+patients were characterized by a higher neutrophil count at admission, 11999 (7568–15747) vs. 8676 (5086–12990) $10^3$cell/mm$^3$, $p=0.040$). Within the CS+group, no differences in 30-day mortality were found according to severity of CAP (non-severe CAP 7% vs. severe CAP c14% $p>0.999$), etiology group (virus only 5% vs. bacterial co-infection 10%, $p>0.999$), influenza virus compared with non-influenza virus (influenza virus 10% vs. non-influenza virus 6%, $p>0.999$). The 3:1 propensity matching procedure identified 90 patients not treated with corticosteroid (CS-) as controls. There were no clinically relevant differences between cohorts after the procedure. See supplementary Fig. 3, for further details on propensity-matching results.

### Primary outcome

At 30 days, two out of 30 CS+patients had died (7%, 95% CI 1 to 22%) and 25 out of 493 CS- patients (5%, 95%CI 3 to 7%), $p=0.663$, see Table 1).

Considering matched cohorts, two out of 30 CS+patients (7%, 95%CI 1 to 22%) and four out of 90 CS- patients (4%, 95%CI 1 to 11%) had died at 30 days ($p=0.639$). Supplementary Fig. 2 shows Kaplan-Meier curves of 30-day survival of the matched and unmatched cohorts. Cox regression models did not show significant differences in the risk of death at 30 days in unmatched and matched cohorts (Hazard Ratio[HR] 1.33 (0.32 to 5.63), $p=0.695$ and HR 1.51 (0.28 to 8.27), $p=0.632$, respectively). Nor was any difference in the risk of death at 30 days observed in a subgroup matched analysis in CS+patients with bacterial co-infection pneumonia (HR 1.57 (0.14 to 17.33), $p=0.713$) vs. CS+patients with exclusively viral pneumonia (HR 1.48 (0.13 to 16.36), $p=0.748$); see Table 2.

### Secondary outcomes

No differences in hospital length of stay, ICU admission and length of stay, mechanical ventilation requirement and duration were detected between matched and unmatched CS+and CS- cohorts (Table 1). Survival analysis did not show differences in in-hospital and 1-year mortality (Tables 1 and 2).

## Discussion

The main finding of our study is the lack of any significant differences in the primary and secondary outcomes regarding the use of corticosteroids in patients with viral pneumonia. Thirty-day mortality was higher in patients who received corticosteroids as adjunctive therapy than in patients who did not, although the difference was not statistically significant, and we also observed potential differences in the impact of corticosteroids in patients with exclusively viral infection and with bacterial co-infection.

Respiratory viruses are identified in between 10% and 20% of adults hospitalized for severe pneumonia, the most frequently reported being influenza viruses [14, 15]. In our study, influenza virus A and B were the most commonly identified (56%). Although scientific evidence supports the use of corticosteroids in patients affected with severe infection caused by SARS-CoV-2 [16], studies in severe influenza pneumonia have observed an association between the use of corticosteroids and a higher mortality rate, longer ICU stay, and an increased rate of secondary infection [9, 10, 17]. At present, there are no randomized clinical trials that have evaluated the use of corticosteroids as adjunctive therapy in patients with influenza CAP. The main evidence for the use of corticosteroids in viral pneumonia comes data from observational and meta-analysis studies. In fact, a study that included 1,846 critically ill patients with influenza pneumonia reported that approximately one-third received corticosteroids, which was associated with increased ICU mortality [18]. Similar results were reported by three systemic reviews and meta-analyses which observed an association between the use of corticosteroids and higher mortality in patients with influenza infection [19–21]. This poor clinical outcome observed in patients with viral pneumonia receiving corticosteroids may have been due to immunosuppression that causes prolonged viremia, higher rates of secondary infections or adverse events related to the use of corticosteroids [5]. We found higher 30-day mortality in patients who received corticosteroids as adjunctive therapy compared to patients who did not. Unfortunately, we cannot draw any firm conclusions regarding corticosteroid use due to the retrospective nature of our study and due to the small sample size. However, corticosteroids have been shown to be beneficial in patients with septic shock and ARDS. In our study, only 4% of patients had septic shock, and 5% had ARDS, a circumstance that may partially explain our results [22, 23]. Interestingly, we did not observe differences in the risk of death at 30 days between CS+patients with bacterial co-infection pneumonia and patients with exclusive viral pneumonia.

The present study has several limitations. First, the observational design means that patients may have received corticosteroids for a reason other than severe pneumonia. Second, in this study, we are unable to address the heterogeneity in the prescription of corticosteroids in terms of time until first dose, total dose, and type of corticosteroids; recent studies have shown that these features may have an important impact on outcomes in patients with severe CAP [24, 25]. Third, due to the small number of patients who received corticosteroids, this study may have been underpowered to detect any difference in the outcomes. Finally, despite the scientific evidence of the possible side effects of corticosteroids [26] such as hyperglycaemia, secondary infection, myopathy, and so on, we did not record these data in our study.

In the light of our results, future studies should investigate the possible presence of significant differences by considering cases of exclusive viral infection and those with bacterial co-infection separately. Studies such as randomized controlled trials are needed to investigate the role of corticosteroids in viral pneumonia.

**Table 1** Characteristics of the study population

| | **Full cohort (*N* = 524)** | | | **Propensity score matching (*N* = 120)** | | |
|---|---|---|---|---|---|---|
| **Variable** | **No systemic corticosteroids treatment (*n* = 494)** | **Systemic corticosteroids treatment (*n* = 30)** | ***P*-value** | **No systemic corticosteroids treatment (*n* = 90)** | **Systemic corticosteroids treatment (*n* = 30)** | ***P*-value** |
| Age, mean (Q1; Q3), years | 71 (55; 81) | 69.5 (54; 80) | 0.773 | 74.5 (61; 82) | 69.5 (54; 80) | 0.489 |
| Male sex, n (%) | 286 (58) | 13 (43) | 0.118 | 36 (40) | 13 (43) | 0.748 |
| Current smoker, n (%) | 112 (23) | 5 (17) | 0.437 | 14 (16) | 5 (17) | > 0.999 |
| Current alcohol use, n (%) | 57 (12) | 2 (7) | 0.560 | 8 (9) | 2 (7) | > 0.999 |
| Previous antibiotic, n (%) | 129 (27) | 10 (34) | 0.408 | 25 (29) | 10 (34) | 0.559 |
| Influenza vaccine, n (%) | 192 (43) | 16 (59) | 0.091 | 48 (59) | 16 (59) | 0.947 |
| Pneumococcal vaccine, n (%) | 107 (24) | 5 (19) | 0.535 | 29 (35) | 5 (19) | 0.109 |
| Previous inhaled corticosteroids, n (%) | 82 (17) | 8 (28) | 0.137 | 27 (30) | 8 (28) | 0.778 |
| Previous episode of pneumonia, n (%) | 79 (16) | 6 (21) | 0.606 | 21 (25) | 6 (21) | 0.660 |
| Comorbidities, n (%) [a] | 337 (69) | 22 (73) | 0.589 | 71 (79) | 22 (73) | 0.528 |
| Chronic respiratory disease | 200 (41) | 11 (37) | 0.602 | 34 (39) | 11 (37) | 0.815 |
| Chronic cardiovascular disease | 58 (12) | 7 (23) | 0.084 | 22 (24) | 7 (23) | 0.902 |
| Diabetes mellitus | 106 (22) | 10 (33) | 0.144 | 30 (34) | 10 (33) | 0.940 |
| Neurologic disease | 74 (15) | 5 (17) | 0.796 | 19 (22) | 5 (17) | 0.793 |
| Chronic renal disease | 46 (9) | 5 (17) | 0.202 | 14 (16) | 5 (17) | > 0.999 |
| Chronic liver disease | 24 (5) | 2 (7) | 0.656 | 7 (8) | 2 (7) | > 0.999 |
| Previous neoplasm | 46 (10) | 3 (11) | 0.746 | 9 (10) | 3 (11) | > 0.999 |
| Nursing home, n (%) | 27 (5) | 2 (7) | 0.680 | 7 (8) | 2 (7) | > 0.999 |
| Cough n (%) | 398 (81) | 22 (79) | 0.727 | 68 (76) | 22 (79) | 0.812 |
| Purulent sputum, n (%) | 271 (57) | 15 (54) | 0.746 | 50 (57) | 15 (54) | 0.763 |
| Dyspnoea, n (%) | 344 (71) | 21 (72) | 0.838 | 65 (74) | 21 (72) | 0.878 |
| Pleuritic pain, n (%) | 131 (27) | 12 (43) | 0.070 | 23 (26) | 12 (43) | 0.100 |
| Fever, n (%) | 372 (76) | 20 (69) | 0.386 | 59 (66) | 20 (60) | 0.735 |
| Confusion, n (%) | 63 (13) | 3 (10) | > 0.999 | 13 (15) | 3 (10) | 0.758 |
| C-reactive protein at baseline, median (Q1; Q3), mg/dL | 17.8 (9.5; 27) | 15.8 (8.6; 23.9) | 0.194 | 17.3 (6.4; 25) | 15.8 (8.6; 23.9) | 0.744 |
| Neutrophils at baseline, median (Q1; Q3), cell/mm$^3$ | 8,676 (5,086; 12,990) | 11,999 (7,568; 15,747) | **0.040** | 9,275 (5,576; 16,237) | 11,999 (7,568; 15,747) | 0.391 |
| Lymphocytes at baseline, median (Q1; Q3), cell/mm$^3$ | 819 (522; 1,330) | 848 (508; 1,440) | 0.802 | 988 (623; 1,449) | 848 (508; 1,440) | 0.785 |
| $PaO_2/FiO_2$, median (Q1; Q3) | 276 (229; 325) | 286 (238; 324) | 0.377 | 271 (229; 351) | 286 (238; 324) | 0.707 |
| PSI score, median (Q1; Q3) | 95 (71; 119) | 81 (55; 124) | 0.498 | 100.5 (80; 122) | 81 (55; 124) | 0.163 |
| PSI risk class IV-V, n (%) [b] | 176 (56) | 9 (45) | 0.335 | 34 (64) | 9 (45) | 0.138 |
| SOFA score, median (Q1; Q3) | 2 (1; 3) | 2 (1; 4) | 0.994 | 2 (1; 3) | 2 (1; 4) | 0.443 |
| Severe CAP, n (%) | 105 (29) | 7 (32) | 0.747 | 20 (27) | 7 (32) | 0.687 |
| Bacteraemia, n (%) [c] | 39 (10) | 2 (9) | > 0.999 | 5 (8) | 2 (9) | > 0.999 |
| Pleural effusion, n (%) | 49 (10) | 2 (7) | > 0.999 | 8 (9) | 2 (7) | > 0.999 |
| Multilobar involvement, n (%) | 147 (30) | 11 (37) | 0.418 | 22 (24) | 11 (37) | 0.194 |
| ARDS, n (%) | 24 (5) | 1 (4) | > 0.999 | 3 (3) | 1 (4) | > 0.999 |
| Acute renal failure, n (%) | 135 (28) | 9 (31) | 0.704 | 25 (28) | 9 (31) | 0.761 |
| Septic shock, n (%) | 21 (4) | 2 (7) | 0.343 | 5 (6) | 2 (7) | 0.664 |
| Empiric antibiotic therapy, n (%) | | | | | | |
| Monotherapy | 159 (33) | 12 (41) | 0.344 | 31 (35) | 12 (41) | 0.551 |
| Fluoroquinolones | 120 (25) | 6 (21) | 0.618 | 25 (28) | 6 (21) | 0.414 |
| β-lactams | 35 (7) | 6 (21) | **0.021** | 6 (7) | 6 (21) | 0.070 |
| Other therapy | 4 (1) | 0 (0) | > 0.999 | 0 (0) | 0 (0) | > 0.999 |
| Combination therapies | 325 (67) | 17 (59) | 0.344 | 57 (65) | 17 (59) | 0.551 |
| β-lactams plus fluoroquinolones | 106 (22) | 6 (21) | 0.878 | 14 (16) | 6 (21) | 0.575 |
| β-lactams plus macrolides | 176 (36) | 6 (21) | 0.087 | 35 (40) | 6 (21) | 0.074 |

**Table 1** (continued)

| | Full cohort (*N* = 524) | | | Propensity score matching (*N* = 120) | | |
|---|---|---|---|---|---|---|
| **Variable** | **No systemic corticosteroids treatment (*n* = 494)** | **Systemic corticosteroids treatment (*n* = 30)** | ***P*-value** | **No systemic corticosteroids treatment (*n* = 90)** | **Systemic corticosteroids treatment (*n* = 30)** | ***P*-value** |
| Other combination therapies | 43 (9) | 5 (17) | 0.176 | 8 (9) | 5 (17) | 0.304 |
| Appropriate empiric treatment, n (%) | 387 (93) | 19 (83) | 0.077 | 64 (91) | 19 (83) | 0.256 |
| Length of hospital stay, median (Q1; Q3), days | 7 (5; 12) | 8 (6; 15) | 0.220 | 7 (5; 11) | 8 (6; 15) | 0.155 |
| ICU admission, n (%) | 115 (23) | 9 (30) | 0.531 | 19 (21) | 9 (30) | 0.709 |
| ICU mortality, n (%) [d] | 8 (7) | 0 (0) | > 0.999 | 1 (5) | 0 (0) | > 0.999 |
| Length of ICU stay, median (Q1; Q3), days [d] | 14 (10; 24.5) | 15 (9; 17) | 0.671 | 15 (9; 24) | 15 (9; 17) | 0.571 |
| Mechanical ventilation, n (%) [e] | | | 0.595 | | | 0.469 |
| Non-invasive | 19 (5) | 2 (8) | 0.331 | 2 (3) | 2 (8) | 0.247 |
| Invasive | 44 (10) | 2 (8) | > 0.999 | 6 (8) | 2 (8) | > 0.999 |
| In-hospital mortality, n (%) | 32 (6) | 2 (7) | > 0.999 | 3 (3) | 2 (7) | 0.598 |
| 30-day mortality, n (%) | 25 (5) | 2 (7) | 0.663 | 4 (4) | 2 (7) | 0.639 |
| 1-year mortality, n (%) | 40 (8) | 3 (11) | 0.722 | 6 (7) | 3 (11) | 0.686 |

*Abbreviations* ARDS indicates acute respiratory distress syndrome; CAP, community-acquired pneumonia; ICU, intensive care unit; PSI, Pneumonia Severity Index; Q1, first quartile; Q3, third quartile. Percentages calculated with non-missing data only. [a] Possibly > 1 comorbidity. [b] Stratified by 30-day mortality risk for CAP: classes I–III (≤ 90 points) had low mortality risk, whilst classes IV–V (> 90 points) had the highest mortality risk. [c] Calculated only for patients with blood samples. [d] Calculated only for patients admitted to intensive care. [e] Patients who initially received non-invasive ventilation yet subsequently needed intubation were included in the invasive mechanical ventilation group. *p*-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit

**Table 2** Cox regression models evaluating the risk of mortality in the systemic corticosteroids treatment group

| Variable | HR | 95% CI | *P*-value |
|---|---|---|---|
| In-hospital mortality | | | |
| Crude (full cohort) (*n* = 524) | 0.97 | 0.23 to 4.10 | 0.972 |
| Etiology group | | | 0.800[a] |
| Only respiratory virus (*n* = 372) | 0.90 | 0.12 to 6.85 | 0.919 |
| Respiratory virus plus bacterial (*n* = 152) | 1.21 | 0.16 to 9.33 | 0.857 |
| Propensity score matching (*n* = 120) | 1.58 | 0.26 to 9.50 | 0.617 |
| Etiology group | | | 0.989[a] |
| Only respiratory virus (*n* = 79) | 1.47 | 0.09 to 23.61 | 0.785 |
| Respiratory virus plus bacterial (*n* = 41) | 1.83 | 0.16 to 21.10 | 0.628 |
| 30-day mortality | | | |
| Crude (full cohort) (*n* = 524) | 1.33 | 0.32 to 5.63 | 0.695 |
| Etiology group | | | 0.952[a] |
| Only respiratory virus (*n* = 372) | 1.25 | 0.16 to 9.51 | 0.829 |
| Respiratory virus plus bacterial (*n* = 152) | 1.35 | 0.17 to 10.48 | 0.773 |
| Propensity score matching (*n* = 120) | 1.51 | 0.28 to 8.27 | 0.632 |
| Etiology group | | | 0.963[a] |
| Only respiratory virus (*n* = 79) | 1.48 | 0.13 to 16.36 | 0.748 |
| Respiratory virus plus bacterial (*n* = 41) | 1.57 | 0.14 to 17.33 | 0.713 |
| 1-year mortality | | | |
| Crude (full cohort) (*n* = 524) | 1.27 | 0.39 to 4.60 | 0.688 |
| Etiology group | | | 0.640[a] |
| Only respiratory virus (*n* = 372) | 1.56 | 0.37 to 6.64 | 0.544 |
| Respiratory virus plus bacterial (*n* = 152) | 0.86 | 0.11 to 6.48 | 0.885 |
| Propensity score matching (*n* = 120) | 1.55 | 0.39 to 6.20 | 0.536 |
| Etiology group | | | 0.663[a] |
| Only respiratory virus (*n* = 79) | 2.05 | 0.34 to 12.27 | 0.433 |
| Respiratory virus plus bacterial (*n* = 41) | 1.05 | 0.11 to 10.13 | 0.964 |

*Abbreviations* HR indicates hazard ratio; CI indicates confidence interval. [a] Interaction effect for the etiology group and systemic corticosteroids treatment group

**Abbreviations**

| | |
|---|---|
| CAP | Community-Acquired Pneumonia |
| CS- | Cohort of patients who did not receive corticosteroids |
| CS+ | Cohort of patients who received corticosteroids |
| RT-PCR | Reverse-Transcriptase Polymerase Chain Reaction |
| IFA | Immunofluorescence |
| PSM | Propensity Score Matching |
| PSI | Pneumonia Severity Score |
| HR | Hazard Ratio |
| CI | Confidence Interval |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41479-024-00146-8.

Supplementary Material 1

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**Author contributions**
Conceptualization and methodology: CC, AG, AG, MA, AT, Data curation and investigation: CC, AG, DC, Writing—original draft. CC, DC, AG, MA, AT: Writing -review & editing: CC, AG, DC, AT.

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**Data availability**
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the Ethics Committees (Register: 2009/5451). Patient identification remained anonymous and informed consent was waived due to the observational nature of the study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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