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MAJOR ARTICLE

Lower Mortality Associated With Adjuvant Corticosteroid Therapy in Non-HIV-Infected Patients With *Pneumocystis jirovecii* Pneumonia: A Single-Institution Retrospective US Cohort Study

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Background. *Pneumocystis jirovecii* pneumonia (PJP) remains a cause of mortality in HIV-negative patients. The clinical benefit of adjuvant corticosteroids in these patients is uncertain. This study aimed to determine if corticosteroids would reduce mortality in a cohort of HIV-negative PJP patients.

Methods. We examined a retrospective case series of patients diagnosed with PJP at the University of Colorado Hospital between 1995 and 2019. Data were collected in 71 PJP-infected patients. Twenty-eight patients were HIV-negative, and 43 were infected with HIV. We performed bivariate and forward, stepwise multivariable logistic regressions to identify mortality predictors.

Results. Common underlying conditions in HIV-negative patients were hematologic malignancies (28.6%), autoimmune disorders (25.9%), and solid organ transplantation (10.7%). HIV-negative patients had higher rates and durations of mechanical ventilation and intensive care unit stay. Survival was significantly increased in HIV-negative patients receiving adjuvant corticosteroids, with 100% mortality in patients not receiving corticosteroids vs 60% mortality in patients receiving corticosteroids ($P = .034$). In an adjusted multivariable model, no adjuvant corticosteroid use was associated with higher mortality (odds ratio, 13.5; 95% CI, 1.1–158.5; $P = .039$) regardless of HIV status.

Conclusions. We found substantial mortality among HIV-negative patients with PJP, and adjuvant corticosteroid use was associated with decreased mortality. Response to corticosteroids is best established in HIV-infected patients, but emerging reports suggest a similar beneficial response in PJP patients without HIV infection. Further prospective studies may establish a more definitive role of the addition of corticosteroids among HIV-negative patients with PJP.

Keywords. HIV negative; *Pneumocystis jirovecii* pneumonia; prognosis; retrospective corticosteroid adjuvant therapy.

Pneumocystis jirovecii is the causative agent of *Pneumocystis jirovecii* pneumonia (PJP). This opportunistic infection affects mainly immunocompromised individuals. In HIV-positive patients, highly active antiretroviral therapy (HAART) and antimicrobial prophylaxis in high-risk patients have substantially lowered the incidence and mortality of PJP. PJP also occurs in HIV-uninfected immunocompromised patients, and in this population, PJP mortality has been increasing [1, 2]. Mortality attributable to PJP in patients with HIV ranges between 10% and 20%, while mortality in HIV-negative patients ranges between 30% and 50% [3–5]. Mortality in PJP-infected patients (with or without HIV infection) is associated with acute lung injury occurring at the time of PJP antimicrobial treatment that damages lung tissues and results in oxygenation failure [6]. The role of oxygenation defect in PJP pathogenesis is underscored by the observation that PJP patients requiring mechanical ventilation (MV) have a worse prognosis compared with patients who only require noninvasive positive pressure ventilation (NPPV) [6–8]. In HIV-positive patients treated with trimethoprim-sulfamethoxazole (TMP-SMX), there is an established role for concomitant adjuvant corticosteroids in reducing respiratory failure or death [9].

Guidelines to treat HIV-positive patients with PJP describe clear criteria for the use of adjuvant corticosteroids [10]. These criteria emphasize corticosteroid use in patients with a severe gas-exchange compromise and associated oxygenation defect.

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On the other hand, there are no accepted guidelines for adjuvant corticosteroid use in treating PJP in HIV-negative patients. An increasing number of studies have examined the use of glucocorticoid steroids in PJP patients without HIV. These studies have shown mixed results, with some showing mortality reduction and others showing no impact [3, 11–14]. The role of adjuvant corticosteroids in HIV-negative patients with PJP is unclear and warrants further investigation [15, 16]. A low prevalence of these patients hampers investigations designed to establish the role of adjuvant corticosteroid efficacy in HIV-negative persons. A definitive understanding of the effectiveness of corticosteroids in these patients necessitates randomization to corticosteroid use or placebo. Collecting sufficient patients for this kind of definitive study is not feasible, as this would require excessively prolonged periods of subject accrual and multi-institution enrollment. Therefore, studies of adjuvant corticosteroid use in PJP patients without HIV infection comprise retrospective case series where corticosteroids were administered without randomization. We aim to identify clinical predictors associated with mortality in a retrospective cohort of PJP cases.

METHODS

Patient Consent Statement

The present project is in Health Insurance Portability and Accountability Act (HIPAA) compliance according to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado Denver. Analysis of clinical data was performed under an approved protocol (COMIRB Protocol 18–2577).

Patients and Data Collection

All PJP cases at the University of Colorado Hospital (UCH) in the period of 1995–2019 were identified through microbiology laboratory records. All cases had a positive *Pneumocystis jirovecii* direct fluorescent assay test in a respiratory sample. Seventy-one cases were identified. A comprehensive review of medical charts and reports was conducted to collect clinical and laboratory data. The following data were collected: demographics (gender, race, age, and occupation); symptoms and signs (body aches, fatigue, cough, dyspnea, fever, and other reports); possible PJP risk factors (smoking, lung disease, diabetes mellitus, malignancy, sarcoidosis, cirrhosis, HIV infection, solid organ transplantation, use of calcineurin inhibitors, or corticosteroids and dose); HIV infection details (time since diagnosis, history of HIV antiretroviral drug resistance, antiretroviral therapy, CD4 count, and viral load); transplantation (type and time since transplant), laboratory results (complete cell count, comprehensive metabolic panel, baseline renal function), and outcomes of PJP infection. We also recorded the need for mechanical ventilation, intensive care unit (ICU) entry and duration, mortality at 30 days, 90 days, and at 1 year, hospital readmission, hospitalization duration, relapse, and immune reconstitution syndrome (IRS). The Colorado Death Registry was automatically interrogated for date and cause of death using a software supported by the Health Data Compass Data Warehouse project (healthdatacompass.org). See Supplementary Appendix A for specific variable definitions.

Statistical Analysis

Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). The means and standard deviations for continuous variables were calculated. For categorical variables, frequencies and percentages were calculated. We initially performed bivariate analyses for dichotomous outcome variables using chi-square testing, and Fisher exact tests were used for dichotomous and nominal independent variables, respectively. For interval-independent variables, we used the *t* test. For multivariable analysis, we selected variables associated with outcome *P* values ≤.05 and included variables previously reported to be associated with outcome or known to be confounders. We did not include co-linear variables or variables with missing significant data. For the incorporation of variables, we transformed nominal and ordinal variables into dichotomous variables. We determined if interval variables were normally distributed by performing the Shapiro-Wilk test. If data for a variable were not normally distributed, the variable was log-transformed or converted into a dichotomous variable. Selected variables were included in a multivariable, forward, stepwise logistic regression model. A parallel conditional logistic regression model was run for comparison. Multivariable analysis was performed for survivors vs nonsurvivors.

Data Access

The corresponding author had full access to data in the study and had final responsibility for the decision to submit the manuscript for publication. The data sets generated that were analyzed in the current study are available from the corresponding author on reasonable request.

RESULTS

Clinical Characteristics of HIV-Negative Patients With PJP

We identified 71 cases with PJP, including 28 HIV-negative patients and 43 HIV-positive patients (Table 1A). Compared with HIV-positive patients, HIV-negative PJP patients were older, demonstrated a slight male predominance, were mostly Caucasian, and lived in the Denver metropolitan area. HIV-positive PJP patients were more likely Hispanic. HIV-positive and HIV-negative groups presented with constitutional symptoms that included dyspnea, cough, fever, and fatigue. HIV-negative patients presented with fewer days of symptoms before admission compared with HIV-positive patients. Solid tumors, inflammatory diseases, and immunosuppressive

Table 1A. Clinical Features of the Cohort of Patients Diagnosed With *Pneumocystis* Pneumonia

		Count (%) or Mean ± SD		
Patient Characteristics	No.	HIV (+) (n = 43)	HIV (-) (n = 28)	*P* Values
Demographics				
Gender (male)	71	38 (88.37)	15 (53.57)	.001
Race (White)	71	31 (72.09)	23 (82.14)	.853
Hispanics	71	11 (25.58)	4 (14.29)	.009
Age	71	49.12 ± 10.97	62.07 ± 13.66	<.0001
Symptoms				
Fatigue	70	26 (60.47)	21 (77.78)	.133
Cough	71	36 (83.72)	14 (50.00)	.002
Dyspnea	71	36 (83.72)	22 (78.57)	.584
Fever	71	31 (72.09)	16 (57.14)	.193
Other	71	37 (86.05)	11 (39.29)	<.0001
Duration of symptoms	71			.028
<1 wk		14 (32.56)	13 (46.43)	
1–4 wk		14 (32.56)	13 (46.43)	
>4 wk		15 (34.88)	2 (7.14)	
Underlying conditions				
Smoking (ever)	71	21 (48.84)	11 (39.29)	.4292
ESRD	71	0 (0)	4 (14.29)	.021
History of OIs	70	18 (41.86)	4 (14.81)	.018
HIV	71			
New HIV Dx		18 (41.86)	NA	NA
In HIV care		17 (39.53)	NA	NA
Cancer	71	1 (2.33)	5 (17.86)	.032
AID	70	1 (2.33)	7 (25.93)	.004
SOT	71	0 (0)	3 (10.71)	.057
Hematologic malignancy	71	1 (2.33)	8 (28.57)	.002
Immunosuppressive	71	2 (4.65)	16 (57.14)	<.0001
Vitals signs				
BMI, kg/m^2	67	23.64 ± 4.41	24.66 ± 3.30	.328
Respiratory rate	70	19.12 ± 4.58	20.52 ± 5.24	.243
Heart rate	71	101.40 ± 20.79	94.43 ± 21.29	.176
SBP, mmHg	71	117.91 ± 18.04	113.39 ± 17.80	.304
DBP, mmHg	71	69.60 ± 11.99	66.61 ± 12.69	.318
O2 sat, %	71	90.98 ± 8.74	92.14 ± 4.98	.524
Temperature, °C	71	37.50 ± 1.15	36.66 ± 0.69	<.001
Laboratory data				
Fi02 (%)	47	32.82 ± 21.42	54.37 ± 32.86	.009
PaO2 <70 mmHg	56	17 (53.13)	18 (75.00)	.094
A-a gradient	60	5.83 ± 10.9	17.7 ± 16.9	.001
PaO2/FiO2 ratio	47	241.1 ± 100.2	172.8 ± 85.3	.019
WBC, $10^9/L$	70	6.90 ± 2.91	8.73 ± 4.71	.074
Hemoglobin, g/dL	70	12.98 ± 2.25	10.9 ± 2.24	<.001
Platelets, $10^9/L$	70	271.36 ± 127.86	141.28 ± 85.13	<.0001
CD4, cells/μL	41	70.4 ± 75.1	NA	NA
HIV viral load, 10^3 copies/mL	42	682.9 ± 159.8	NA	NA
Lymph, $10^9/L$	66	1.34 ± 0.90	0.78 ± 0.72	.011
Na, mmol/L	71	134.63 ± 3.48	134.04 ± 6.13	.645
Creatinine, mg/dL	71	0.94 ± 0.27	1.37 ± 1.06	.047
Alk phos, U/L	66	82.2 ± 67.4	122.2 ± 115.2	.08
LDH, U/L	70	408.5 ± 313	410.3 ± 163	.97
ALT, U/L	66	34.31 ± 30.38	77.9 ± 148.9	.08
Albumin, g/dL	67	2.99 ± 0.75	2.57 ± 0.66	.02
Treatments				
Corticosteroids	71	37 (86.05)	20 (71.43)	.13
TMP-SMX	71	38 (88.4)	22 (78.6)	.265
TMP-SMX IV	71	9 (21)	6 (21.4)	.96

Table 1A. Continued

Patient Characteristics	No.	Count (%) or Mean ± SD		*P* Values
		HIV (+) (n = 43)	HIV (-) (n = 28)	
Atovaquone	71	2 (4.6)	1 (3.6)	.825
Outcomes				
MV	70	5 (11.90)	17 (60.71)	<.0001
ICU stay	71	10 (23.26)	22 (78.57)	<.0001
Mortality	71	7 (16.28)	20 (71.43)	<.0001
90-d mortality	69	3 (7.14)	16 (59.26)	<.0001
1-y mortality	64	3 (7.69)	19 (76.00)	<.0001

Abbreviations: AID, autoimmune disease; ALT, alanine aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; ESRD, end-stage renal disease; ICU, intensive care unit; IV, intravenous; LDH, lactate dehydrogenase; MV, mechanical ventilation; N/A, not applicable; OI, opportunistic infection; SBP, systolic blood pressure; SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole.

medications were more common in HIV-negative patients with PJP. Laboratory data in HIV-negative patients were notable for normal-range means for leukocytes and sodium. LDH was similarly elevated in both groups. HIV-negative patients had mild thrombocytopenia, lymphopenia, an upper limit of normal creatinine, increased liver enzymes, and low albumin. Compared with HIV-positive patients, HIV-negative patients' admission clinical data revealed an increased prevalence of hypoxia, higher FiO2 requirements, and higher A-a gradients compared with HIV-positive PJP patients. HIV-negative patients had higher rates of mechanical ventilation, mortality during hospitalization, and 1-year mortality. The overall mortality rate was significantly higher in PJP cases without HIV (71.4%) than in PJP patients with HIV (16.3%) (Table 1A). Kaplan-Meier survival curves demonstrated a steep rapid onset of decreased survival among HIV-negative patients compared with HIV-positive patients (Figure 1). Death registry interrogation revealed that PJP was the cause of death in 80% of HIV-negative patients, making PJP the leading case of death in this group. In contrast, PJP was listed as the cause of death in 43% of HIV-positive patients. Adjuvant corticosteroid administration in HIV-negative patients had a marked effect on mortality. Mortality in HIV-negative patients who received adjuvant corticosteroid therapy was 60%, compared with 100% mortality in HIV-negative patients who did not receive corticosteroids ($P = .034$) (Figure 2). There was no statistically significant difference in the percentage of patients receiving adjuvant corticosteroids in patients with or without HIV.

Clinical Outcomes and Predictors of Mortality in the Total Cohort of 71 PJP Cases

Survivors were younger (51.25 ± 11.96), predominantly male (79.55%), and commonly presented with cough and dyspnea (Table 1B). Patients who died tended to present more acutely (fewer days from onset of symptoms to admission), although this was not statistically significant. Survivors and nonsurvivors shared similar comorbidity profiles. However, nonsurvivors had higher rates of hematologic malignancies or being on immunosuppressive medications. Vital signs and oxygen saturation on admission were similar between the groups. FiO_2 and A-a gradients were higher among nonsurvivors compared with survivors. Laboratory studies among nonsurvivors were characterized by an increased presence of anemia, lymphopenia, and hyponatremia, elevated creatinine, and abnormal liver function tests. More survivors than nonsurvivors received adjuvant corticosteroid therapy (Figure 2), and nonsurvivors had higher rates of ICU admission and more frequently received mechanical ventilation. In an adjusted multivariable analysis, HIV infection and the use of adjuvant corticosteroid therapy were independently associated with lower mortality (Supplementary Appendix B). The mortality reduction in HIV-negative patients given adjuvant corticosteroids (40%) was larger than the mortality reduction in HIV-positive patients (20%). A statistically significant mortality reduction associated with adjuvant corticosteroid use was observed only in the HIV-negative subgroup. The mean values for the PaO2/FiO2 ratio among patients who received corticosteroids vs those who did not were 204.2 ± 88.1 and 266.2 ± 146.9 (Table 1B).

DISCUSSION

In our total cohort of 71 PJP patients, we found lower adjusted mortality in patients who received corticosteroids regardless of HIV status. We observed substantial mortality in 28 HIV-negative patients with PJP and a significantly reduced mortality with the use of adjuvant corticosteroids in these patients. Other cohort studies have reported discrepant mortality outcomes for adjuvant steroid use in HIV-negative patients [17, 18]. However, a recent systematic review and meta-analysis of HIV-negative PJP patients found probable benefit for adjuvant corticosteroids restricted to the most severely infected hypoxemic patients [19]. Our study further supports literature showing increased mortality and morbidity in HIV-negative patients with PJP compared with HIV-positive patients [20]. Most PJP-associated mortality among HIV-negative patients occurred shortly after diagnosis. Poorer prognosis in HIV-uninfected patients may be due to the difference in timing and severity of presentation, more severe comorbidities among HIV-negative patients, or increased PJP pathogen density in the lungs. Our study showed

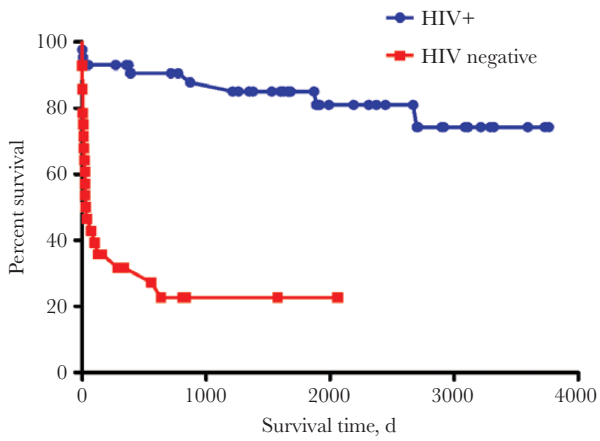
Table 1B. Clinical Features of the Cohort of Patients Diagnosed With *Pneumocystis* Pneumonia

		Count (%) or Mean ± SD					
Patient Characteristics	No.	Alive (n = 44)	Death (n = 27)	*P* Values	No Steroids (n = 14)	Steroids (n = 57)	*P* Values
Demographics							
Gender (male)	71	35 (79.55)	18 (66.67)	.226	12 (85.7)	41 (71.9)	.288
Race (White)	71	32 (72.73)	22 (81.48)	.891	13 (92.7)	41 (71.9)	.532
Hispanics	71	11 (25.00)	4 (14.81)	.069	2 (14.3)	13 (22.8)	.153
Age	71	51.25 ± 11.96	59.08 ± 14.88	.017	51.9 ± 10.5	54.8 ± 14.3	.4864
Symptoms							
Fatigue	70	29 (65.91)	18 (69.23)	.775	10 (71.4)	37 (66.1)	.703
Cough	71	36 (81.82)	14 (51.85)	.007	9 (64.3)	41 (71.9)	.574
Dyspnea	71	39 (88.64)	19 (70.37)	.065	12 (85.7)	46 (80.7)	.664
Fever	71	29 (65.91)	18 (66.67)	.948	7 (50)	40 (70.2)	.153
Other	71	34 (77.27)	14 (51.85)	.026	10 (71.4)	38 (66.7)	.733
Duration of symptoms	71			.171			.801
<1 wk		13 (29.55)	14 (51.85)		6 (42.9)	21 (36.8)	
1–4 wk		19 (43.18)	8 (29.63)		4 (28.6)	23 (40.4)	
>4 wk		12 (27.27)	5 (18.52)		4 (28.6)	13 (22.8)	
Underlying conditions							
Smoking (ever)	71	20 (45.45)	12 (44.44)	.9338	7 (50)	25 (43.9)	.679
ESRD	71	2 (4.55)	2 (7.41)	.632	0 (0)	4 (7)	.308
History of OIs	70	16 (36.36)	6 (23.08)	.247	4 (30.8)	18 (31.6)	.955
HIV	71	36 (81.82)	7 (25.93)	<.0001	6 (42.9)	37 (64.9)	.130
Cancer	71	2 (4.55)	4 (14.81)	.192	0 (0)	6 (10.5)	.205
AID	70	5 (11.36)	3 (11.54)	1	1 (7.7)	7(12.3)	.639
SOT	71	1 (2.27)	2 (7.41)	.553	1 (7.1)	2 (3.5)	.545
Hematologic malignancy	71	3 (6.82)	6 (22.22)	.075	2 (14.3)	7 (12.3)	.840
Immunosuppressive	71	8 (18.18)	10 (37.04)	.076	4 (28.6)	14 (24.6)	.757
Laboratory data							
Fi02, %	47	35.9 ± 24.24	51.47 ± 33	.07	47.7 ± 35.4	40.5 ± 27.4	.53
PaO2 <70 mmHg	56	22 (64.71)	13 (59.09)	.672	3 (30)	32 (69.6)	.01
A-a gradient	60	7.4 ± 12.2	14.8 ± 17.1	.05	8.8 ± 15.6	10.2 ± 14.3	.77
PaO2/FiO2 ratio	47	234.6 ± 96.4	176.2 ± 96.3	.05	266.2 ± 146.9	204.3 ± 88.1	.13
Treatments							
TMP-SMX	71	37 (84.1)	23 (85.2)	.902	11 (78.6)	49 (86)	.493
TMP-SMX IV	71	7 (15.9)	8 (29.6)	.169	2 (14.3)	13 (22.8)	.484
Atovaquone	71	3 (6.8)	0 (0)	.166	0 (0)	3 (5.3)	.380
Outcomes							
MV	70	5 (11.63)	17 (62.96)	<.0001	7 (50)	15 (26.8)	.094
ICU stay	71	14 (31.82)	18 (66.67)	.004	7 (50)	25 (43.9)	.679
Mortality	71	0 (0)	27 (100)	NA	10 (71.4)	17 (29.8)	.004
90-d mortality	69	0 (0)	19 (70.4)	NA	6 (42.9)	13 (23.6)	.151
1-y mortality	64	0 (0)	22 (81.5)	NA	8 (57.1)	14 (28)	.042

Abbreviations: AID, autoimmune disease; BMI, body mass index; ESRD, end-stage renal disease; ICU, intensive care unit; IV, intravenous; MV, mechanical ventilation; N/A, not applicable; OI, opportunistic infection; SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole.

substantial PJP severity in HIV-negative patients, as indicated by elevated A-a gradient and signs of end-organ injury.

Our data also revealed several clinical variables showing that HIV-negative patients tend to present more acutely when seeking care and that their respiratory compromise puts them at higher risk of death. Over the last 2 decades, we have seen some major changes in HIV survival because of modern-day antiretroviral therapies, which have reduced mortality by 10% and 12% for HIV patients with PCP; however, over the same time, HIV-negative patients with PJP have not seen the same decrease in mortality. Although treated similarly, the use of adjuvant corticosteroids regardless of HIV status is not the primary reason for differences in mortality. The mortality found in our cohort among HIV-negative patients of 71% is higher than in other published cohorts (30%–50%). The inclusion of cases from more than 20 years ago and a significant proportion of patients with autoimmune disorders on immunosuppressive medications may partially account for those differences. Although the use of intravenous TMP-SMX delivery can be considered superior to oral administration, we did not observe



Days	0	29	101	339	716	1990	2057	2062
HIV+	43	42	41	40	35	18	18	18
HIV–	28	15	12	8	6	3	2	1

Figure 1. Survival curves based on HIV status in patients with *Pneumocystis jirovecii* pneumonia.

significant differences in the rate of oral or intravenous TMP-SMX use. Data were not available in our cohort to assess differences in outcomes based on the time to diagnosis of PJP disease plus the time to initiate effective therapy. HIV-negative patients typically take a longer time to be diagnosed with PJP infection and to be started on anti-PJP therapy. Baseline differences in pneumonia severity (more severe among HIV-negative patients) likely accounted for the higher mortality in the HIV-negative patients with PJP. Irrespective of steroid therapy administration, HIV-negative patients were sicker, and therefore much more likely to die. Further studies are needed to establish risk factors and cause of mortality differences in HIV-negative patients with PJP.

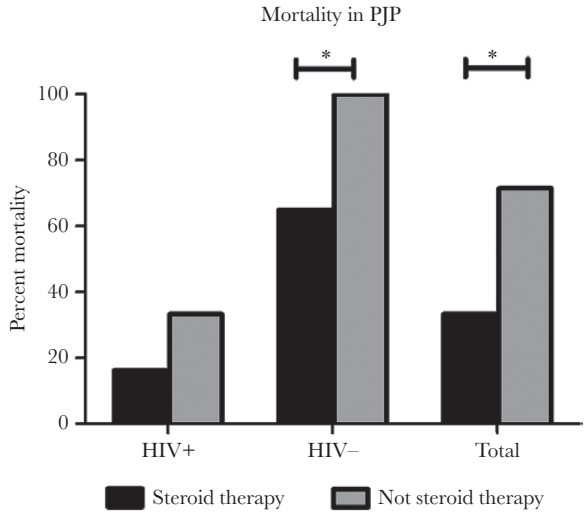


Figure 2. Mortality differences by HIV status and use of steroids in *Pneumocystis jirovecii* pneumonia. *$P \leq .05$. Abbreviation: PJP, *Pneumocystis jirovecii* pneumonia.

The limitations of this study include the retrospective selection of data and the reliability of predictors of the variables analyzed. Selection bias in predictors analyzed may exist, as different observers collected cases. Missing data occurred in medical records and prohibited analysis for some variables. This is a relatively small retrospective cohort that included inherent biases and residual unmeasured confounders that likely affected the results presented. As a result of a small cohort, there was limited statistical power to show clinically significant differences in outcomes. We, however, employed measures to reduce biases by adjusting for confounders. Cohort effects could be another source of a range of potential unmeasured confounders and inherent biases because of changes in standards of care for the treatment of HIV over time and the development of new therapies for solid cancers, autoimmune diseases, and solid organ transplantation. The observational nature, the small sample of HIV-negative patients, and the absence of controls prohibit drawing definite conclusions about the use of steroids in HIV-negative patients.

CONCLUSIONS

HIV-negative PJP patients had significantly increased mortality compared with HIV-infected PJP patients. In the entire cohort, patients who received adjuvant corticosteroids with antimicrobial PJP treatment had significantly lower mortality. HIV-negative patients had more severe disease before antimicrobial therapy. Response to corticosteroids is best established in HIV-infected patients, but emerging reports suggest a similar beneficial response in PJP patients without HIV infection. Further prospective studies may establish a more definitive role of corticosteroid addition among HIV-negative patients with PJP.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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