Corticosteroid exposure as a Risk Factor for *Pneumocystis jirovecii* Pneumonia Mortality in HIV-Negative Patients: A Multicenter Retrospective Case-Control Study with a Global Research Network Validation

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Background

- HIV-negative patients have higher mortality from PJP compared to patients with HIV
- We lack data on predictors of PJP-associated mortality in HIV-negative patients.
- We aim to characterize the role of previous corticosteroid exposure in PJP-related mortality.

Methods

- Multicenter retrospective case-control study was performed on HIV-negative patients tested for PJP from 2000 to 2021.
- Cox proportional-hazards model was used for survival analysis.
- We queried TrinetX, a global research network, to validate mortality risk differences among HIV-negative patients with PJP with prior corticosteroid exposure versus those without.
- We used propensity score matching to assess independent corticosteroid risk of 1-year mortality.

Results

Table 1. UCHealth multicenter HIV-negative patients tested for *Pneumocystis jirovecii* case-control characteristics

Patient characteristic	Controls without PJP (n=105)	PJP Cases (n=71)
Age, years (mean ± SD)	56.7 ± 16.5	64.5 ± 14.6
Male	64 (61%)	39 (54.9%)
White	78 (74.3%)	54 (76.1%)
Smoking history	60 (58.3%)	29 (40.8%)
Liver disease	11 (10.5%)	10 (14.1%)
ESRD	3 (2.9%)	10 (14.1%)
Lung disease	42 (40%)	16 (22.5%)
Autoimmune disease	15 (14.3%)	22 (31.4%)
Solid malignancy	19 (18.1%)	19 (26.8%)
Metastatic	9 (47.4%)	15 (78.9%)
Hematologic malignancy	26 (24.8%)	20 (28.2%)
Solid organ transplant	11 (10.7%)	8 (11.3%)
Stem cell transplant	15 (57.7%)	6 (30%)
Use of immunosuppressants	48 (45.7%)	58 (81.7%)
Azathioprine	0	3 (4.2%)
Mycophenolate mofetil	15 (14.3%)	5 (7%)
Cyclosporine	3 (2.9%)	4 (5.6%)
Disease modifying antirheumatic drugs	6 (5.7%)	7 (9.9%)
Tacrolimus	14 (13.3%)	7 (9.9%)
Mtor inhibitors	3 (2.9%)	3 (4.2%)
Biologics (Rituximab, TNF-alpha inhibitors)	17 (16.2%)	23 (32.4%)
On corticosteroids in prior 6 months	55 (52.4%)	62 (87.3%)
Maintenance	33 (31.4%)	35 (49.3%)
Taper	9 (8.6%)	23 (32.4%)
Burst	18 (17.1%)	21 (29.6%)
Undetermined	6 (5.7%)	9 (12.7%)
Duration of use, weeks (mean ± SD)	15.6 ± 19.3	13.1 ± 9.6
Steroid use >6 months	27 (55.1%)	26 (44.1%)
PED, mg/day (mean ± SD)	18.2 ± 13.1	21.7 ± 15.9
without burst doses, mg/day (mean ± SD)	38.4 ± 53.6	39 ± 44.2
On ≥ 20 pred eq mg/d	19 (18.1%)	41 (57.7%)
On ≥ 25 pred eq mg/d	16 (15.2%)	37 (52.1%)
On PJP prophylaxis	20 (19%)	2 (2.8%)
PJP Test		
DFA	92 (87.6%)	37 (52.1%)
PCR	13 (12.4%)	34 (47.9%)
Source		
Sputum	35 (33.3%)	14 (19.7%)
Tracheal aspirate	3 (2.9%)	1 (1.4%)
Bronchoalveolar lavage	69 (65.7%)	57 (80.3%)
Outcomes		
Mechanical ventilation	37 (64.9%)	26 (72.2%)
Death	60 (57.1%)	43 (60.6%)
In hospitalization	19 (18.1%)	25 (35.2%)
30-day mortality	25 (23.8%)	26 (36.6%)

Note: Corticosteroid use was defined as maintenance= any stable dose >1 month, taper = gradual decrease in steroids spanning >2 weeks, burst= > 60 prednisone equivalent per day for less than 7 days. SD: standard deviation; ESRD: End stage renal disease; DFA= direct fluorescent antibody; PCR= polymerase chain reaction; PED= prednisone equivalent dose;

Table 2. Multivariable Cox proportional hazards model for HIV-negative PJP associated 10-week mortality

Characteristic	HR	95% CI	p-value
Corticosteroids	3.9	1.6-9.4	0.002
Case/Control	1.1	0.6-2	0.768
Age	1	0.9-1.0	0.07
Gender	1.2	0.7-2.1	0.549
Race	0.9	0.7-1.2	0.627
Liver disease	2.8	1.4-5.9	0.005
Lung Disease	0.7	0.4-1.5	0.417
Neoplasia	1	0.5-1.9	0.906
Inflammatory disease	0.6	0.3-1.3	0.197
Solid organ trasplant	0.9	0.4-2.2	0.845
Smoking	0.6	0.3-1	0.061
Immunosuppressive medication	0.4	0.2-0.9	0.031
Hematologic malignancy	1.1	0.5-2.1	0.878

Figure 1. Adjusted 10-week mortality among HIV-negative patients with PJP by corticosteroid exposure

Adjusted Kaplan-Meier survival curve at 70-days by corticosteroid exposure
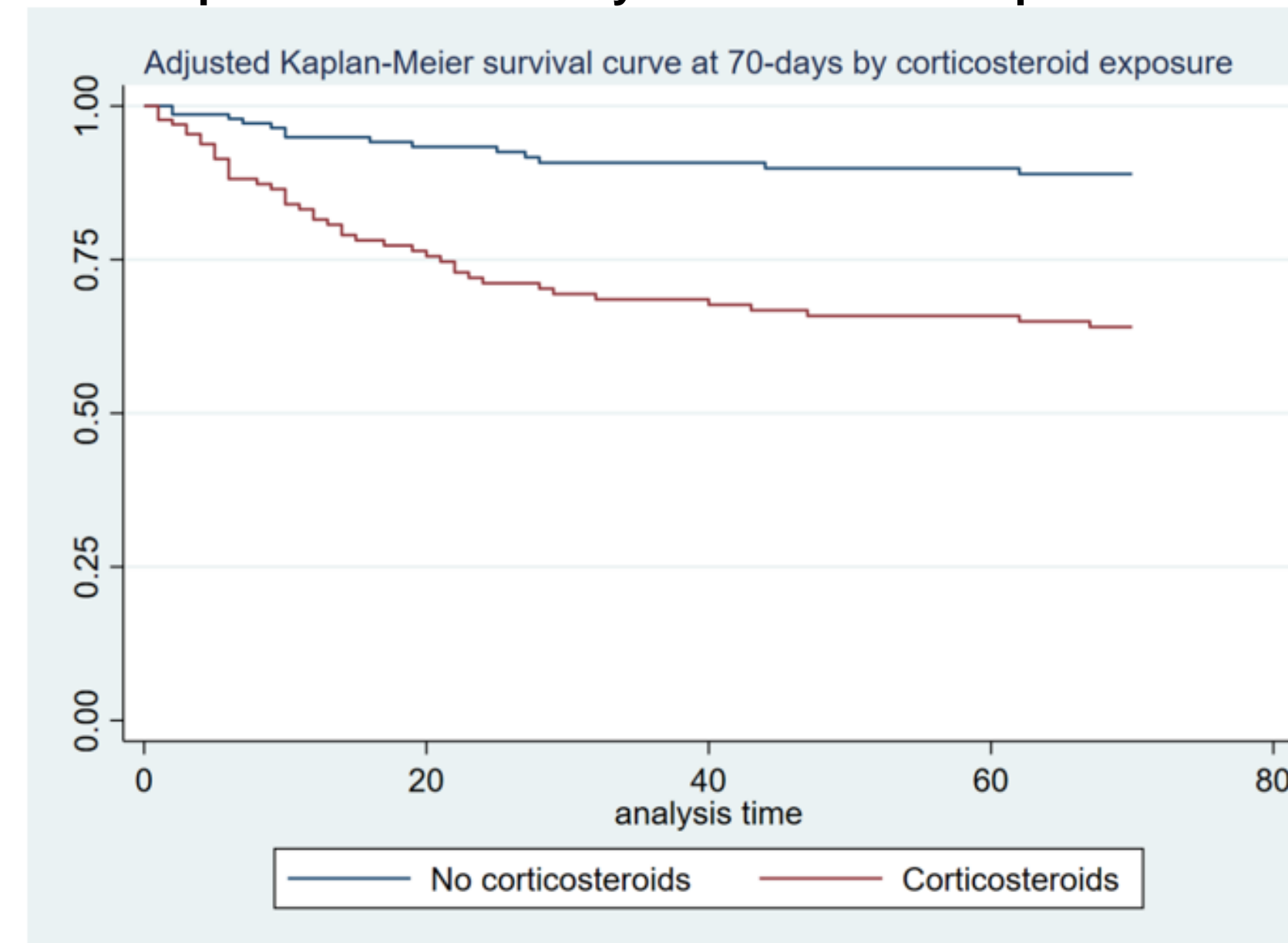
- Previous corticosteroids increased rate of PJP death at 10-weeks (HR: 3.1) and 1-year (HR: 4.1, p<0.0001).
- A TrinetX-based propensity score matching of 2176 HIV-negative patients found a significantly increased 1-year mortality (OR: 1.9 CI: 1.6-2.2, p<0.0001) after PJP diagnoses in the group with corticosteroid exposure in the previous year compared to those with PJP without corticosteroid exposure.

Conclusions

- HIV-negative patients with PJP and corticosteroid use preceding diagnosis have higher mortality than those without corticosteroid use.
- Small percentage of patients at risk on PJP prophylaxis
- Patients with corticosteroid use less than 20 mg PED were also at risk of PJP

Implications

- We recommend having a low threshold to initiate chemoprophylaxis against PJP when corticosteroids are used.
- Use of corticosteroids as part of treatment for PJP in HIV-negative patients, especially those with previous steroid use, needs to be further evaluated.

Disclosures

- None