

Predicting mortality from HIV-associated *Pneumocystis* pneumonia at illness presentation: an observational cohort study

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ABSTRACT

Background: Although the use of antiretroviral therapy has led to dramatic declines in AIDS-associated mortality, *Pneumocystis* pneumonia (PCP) remains a leading cause of death in HIV-infected patients.

Objectives: To measure mortality, identify predictors of mortality at time of illness presentation and derive a PCP mortality prediction rule that stratifies patients by risk for mortality.

Methods: An observational cohort study with case note review of all HIV-infected persons with a laboratory diagnosis of PCP at San Francisco General Hospital from 1997 to 2006.

Results: 451 patients were diagnosed with PCP on 524 occasions. In-hospital mortality was 10.3%. Multivariate analysis identified five significant predictors of mortality: age (adjusted odds ratio (AOR) per 10-year increase, 1.69; 95% CI 1.08 to 2.65; $p = 0.02$); recent injection drug use (AOR 2.86; 95% CI 1.28 to 6.42; $p = 0.01$); total bilirubin >0.6 mg/dl (AOR 2.59; 95% CI 1.19 to 5.62; $p = 0.02$); serum albumin <3 g/dl (AOR 3.63; 95% CI 1.72–7.66; $p = 0.001$); and alveolar–arterial oxygen gradient ≥ 50 mm Hg (AOR 3.02; 95% CI 1.41 to 6.47; $p = 0.004$). Using these five predictors, a six-point PCP mortality prediction rule was derived that stratifies patients according to increasing risk of mortality: score 0–1, 4%; score 2–3, 12%; score 4–5, 48%.

Conclusions: The PCP mortality prediction rule stratifies patients by mortality risk at the time of illness presentation and should be validated as a clinical tool.

In 1996, the approval of HIV protease inhibitors and their use in combination with two nucleoside reverse transcriptase inhibitors heralded the current era of combination antiretroviral therapy (CART) that has witnessed dramatic declines in AIDS-associated mortality.¹ *Pneumocystis* pneumonia (PCP), however, remains the most common AIDS-defining illness in the current era, and is a frequent cause of morbidity and mortality in HIV-infected patients.^{2–3} In the pre-CART era, mortality from PCP ranged from 10% to 30%,^{4–9} with even higher mortality rates of 35–85% in patients requiring admission to an intensive care unit (ICU).^{10–16} In comparison, few studies have examined PCP mortality in the CART era. One study based in North America reported a PCP mortality of 11.6% in the CART era,¹⁷ while a study based in the UK reported a decrease in PCP mortality during the pre-CART to CART eras from 14.8% to 9.7% ($p = 0.142$).¹⁸ None of the patients, however, was receiving CART.¹⁸ Whether mortality from PCP has changed since the introduction of CART is an important, unanswered question.

Previous studies have reported predictors of mortality in HIV-infected patients with PCP. In multivariate analysis, age,^{18–19} alveolar–arterial oxygen gradient (A–a O₂ gradient),^{9, 20} serum albumin,^{12, 17, 20} total lymphocyte count,⁹ haemoglobin,¹⁸ serum lactate dehydrogenase (LDH)⁵ and body mass index⁹ have been reported to be predictors of mortality. Results have been inconsistent, as not all studies were powered to identify each variable (eg, age, PaO₂ or LDH) as predictors of mortality.^{19, 21} In addition, most of these studies were performed before the introduction of CART and included patients who were presumptively diagnosed with PCP without laboratory confirmation.^{9, 22} Finally, some predictors of mortality, such as HIV wasting, are subject to variability in provider interpretation, while others, such as bronchoalveolar lavage (BAL) neutrophilia or pulmonary Kaposi sarcoma, require specialty consultation and bronchoscopy and are therefore only performed in a subset of persons later in the hospital course.^{8, 18, 21} Because of these limitations, clinicians lack a simple tool for stratifying patients with PCP by risk for mortality at illness presentation.

Therefore, we performed a retrospective observational cohort study with case note review of all HIV-infected patients with laboratory-diagnosed PCP at San Francisco General Hospital (SFGH) in the decade immediately after the introduction of CART. Our three goals were to measure in-hospital mortality in the CART era; to identify objective, independent predictors of mortality that are available at the time of illness presentation; and to derive a PCP mortality prediction rule that stratifies patients by risk for in-hospital mortality.

MATERIALS AND METHODS

Patients

Patients were consecutive HIV-infected persons diagnosed with PCP at SFGH between 1 January 1997 and 31 December 2006. PCP was diagnosed by identification of *Pneumocystis* cystic or trophic forms on microscopic examination of Giemsa-stained (Diff-Quik stain, Dade Behring, Newark, Delaware, USA) induced sputum or BAL specimens. We identified PCP cases by reviewing a registry of all diagnostic tests performed for PCP in the Division of Pulmonary and Critical Care Medicine. Because the Pulmonary Division performs all diagnostic procedures (sputum induction and bronchoscopy) for PCP and the standard of care is to confirm the diagnosis of PCP, it is unlikely that any cases were treated empirically or diagnosed without our involvement or knowledge.²³ We confirmed all cases using the SFGH

electronic medical record. The University of California, San Francisco Committee on Human Research approved the study protocol.

Data collection

Data were collected by case note review using standardised abstraction forms and predetermined definitions. Predictor variables consisted of demographic characteristics, medical history, initial vital signs, and laboratory data at presentation. CART was defined as use of at least three antiretroviral agents from two or more drug classes. Mortality was defined as death in the hospital or after transfer to hospice care.

Statistical analysis

Statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, North Carolina, USA). Bivariate and multivariate analyses were performed using logistic regression with mortality as the dependent variable. We used general estimating equations to adjust for clustered values among multiple PCP episodes of the same patient; multiple episodes per patient were ordered by visit date. Predictors with non-normal distribution were dichotomised using cut-off points based on either median or clinically relevant values. We considered all predictors with p values <0.05 in bivariate analysis for inclusion in the multivariate model. However, to avoid a multicollinearity effect with CD4 cell count and A-a O₂ gradient, respectively, total lymphocyte count and oxygen saturation were excluded from the multivariate model. There was a strong positive linear correlation between age and blood urea nitrogen (BUN) (Pearson correlation coefficient = 0.24, $p < 0.001$). Therefore, BUN was excluded from the model because earlier studies have reported age rather than BUN as a predictor of PCP mortality.^{18, 19} To develop the best-fit model, we used stepwise logistic regression and specified a level of significance (α) >0.10 for elimination. To assess for trend in PCP mortality over time, we performed Poisson regression with a variable for calendar year, setting 1997 equal to 0 and increasing the value by 1 for each subsequent year.²⁴ All statistical tests were two-sided; a p value <0.05 was considered statistically significant.

RESULTS

From 1 January 1997 to 31 December 2006, 524 consecutive episodes of PCP were diagnosed in 451 HIV-infected patients at SFGH. Overall, 503 episodes (96%) required hospitalisation and 21 episodes (4%) were treated as outpatients; no subject treated for PCP as an outpatient died in the month following diagnosis. The number of PCP cases per year decreased throughout the study period, from a high of 74 cases in 1998 to a low of 28 cases in 2006. There was no significant change in mortality by study year, which ranged from 5% to 15% ($p = 0.40$). A total of 56 patients had more than one episode of PCP diagnosed during the study period. There was no significant difference in mortality between a first episode of PCP and a repeat episode (11% (48 of 451 first episodes) vs 8% (6 of 73 repeat episodes), respectively, $p = 0.54$).

Demographic and clinical characteristics at admission

The mean age of the cohort was 41 years, and the majority were men (87%) and of non-white race (53%) (table 1). While the main risk factor for HIV infection was being a man who has sex with other men (59%), injection drug use was also common (37%). HIV was newly diagnosed during evaluation for PCP in 121 patients (23%). Patients were severely immunosuppressed

Table 1 Characteristics of 524 HIV-infected patients with *Pneumocystis pneumonia* at San Francisco General Hospital, 1997–2006

Characteristics	Number of cases (%)* (n = 524)
Sociodemographic	
Mean age, years	41 (8)
Male gender	456 (87)
Race	
White	248 (47)
Black	153 (29)
Other	123 (23)
History of tobacco use (n = 504)	347 (69)
History of injection drug use (n = 506)†	
Recent	95 (19)
Past	90 (18)
Never	321 (63)
Homeless (n = 508)	72 (14)
Medical history	
HIV risk factor‡	
Men who have sex with men (n = 454)	268 (59)
Injection drug use (n = 506)	185 (37)
Heterosexual sex (n = 454)	104 (23)
New diagnosis of HIV (n = 522)	121 (23)
Medical co-morbidity§ (n = 524)	293 (56)
History of any opportunistic infection (n = 506)	265 (52)
History of PCP (n = 511)	138 (27)
History of cutaneous, oral or pulmonary KS (n = 524)	31 (6)
Pulmonary KS at admission (n = 172)	10 (6)
CART prior to admission (n = 516)	58 (11)
PCP prophylaxis (n = 515)	75 (15)
Vital signs	
Mean temperature, °C (n = 492)	38.5 (1.0)
Mean pulse, beats/min (n = 492)	107 (18)
Mean systolic blood pressure, mm Hg (n = 491)	107 (15)
Median respiratory rate, breaths/min (n = 492)	22 (20–28)
Median room air oxygen saturation, % (n = 475)	91 (87–95)
Laboratory values	
Median CD4 cell count, cells/ μ l (n = 515)	29 (13–64)
Median HIV viral load, log copies/ml (n = 492)	12.1 (11.2–12.8)
Median total lymphocyte count, 10^9 /l (n = 504)	0.7 (0.4–1.1)
Mean haematocrit, % (n = 522)	34.8 (5.4)
Mean sodium, mmol/l (n = 519)	136 (4)
Median BUN, mg/dl (n = 512)	13 (10–17)
Median creatinine, mg/dl (n = 519)	0.9 (0.8–1.0)
Median INR (n = 268)	1.1 (1.0–1.3)
Median total bilirubin, mg/dl (n = 470)	0.6 (0.4–0.8)
Mean albumin, g/dl (n = 464)	3.1 (0.6)
Median A–a O ₂ gradient, mm Hg (n = 431)	47 (33–61)
Median LDH, U/l (n = 477)	358 (270–503)

*Values are shown as number (%) unless otherwise stated; means are presented with the SD, medians with the IQR.

†Recent injection drug use is defined as drug use during the 6 months before admission; past injection drug use is defined as last drug use >6 months before admission.

‡Total n (%) exceeds 524 (100%) because of 92 patients with multiple HIV risk factors.

§Medical co-morbidity is defined as having a history of opportunistic infection, renal failure (creatinine >1.2 mg/dl) or hepatic insufficiency (INR ≥ 1.2).

A–a O₂ gradient, alveolar–arterial oxygen gradient; BUN, blood urea nitrogen; CART, combination antiretroviral therapy; INR, international normalised ratio; KS, Kaposi sarcoma; LDH, lactate dehydrogenase; PCP, *Pneumocystis pneumonia*.

at presentation, with a median CD4 cell count of 29 cells/ μ l (interquartile range (IQR) 13–64 cells/ μ l). While 52% of patients had a history of opportunistic infection, only 11% were taking CART and 15% were taking PCP prophylaxis. The median CD4 cell count in patients taking CART prior to admission was not significantly different compared with patients not taking CART

(36 vs 28 cells/ μ l, $p = 0.89$). However, patients taking CART had a significantly lower HIV viral load (11.5 vs 12.2 log copies/ml, $p = 0.001$). Of the patients taking CART, 44% had initiated treatment in the 2 months prior to admission. There were no significant differences in admission laboratory indices or hospital outcomes between patients who had recently started CART and those who had not. Laboratory data were characterised by a marked abnormality in gas exchange, with a median A–a O_2 gradient of 47 mm Hg (IQR 33–61 mm Hg).

Hospital course and outcomes

In-hospital mortality was 10.3%. The median length of stay was 8 days (range 2–80 days). The diagnosis of PCP was made by sputum induction in 67% of cases and by BAL in the remaining 33%. The sensitivity of sputum induction for diagnosis of PCP was 73%. Trimethoprim–sulfamethoxazole was the initial antimicrobial therapy for 82% of episodes (402 of 493), and 79% of the patients received adjunctive corticosteroids (390 of 493). A minority of patients were initiated on CART in the hospital (38 of 440; 9%). Only 33 patients developed a pneumothorax, but in-hospital mortality in these patients was high (73%). Overall, 16% of patients required ICU care and 13% required mechanical ventilation. The mortality in these patients was 54% and 65%, respectively.

Predictors of mortality

There were 16 variables at presentation that were significantly associated with mortality in bivariate analysis: age, recent injection drug use during the 6 months before admission, temperature, systolic blood pressure, room air O_2 saturation, CD4 cell count, total lymphocyte count, sodium, BUN, total bilirubin, serum albumin, A–a O_2 gradient, serum LDH, medical co-morbidity, hepatic insufficiency and pneumothorax at admission (table 2). Among events occurring during hospitalisation, requiring intensive care ($p < 0.001$) and mechanical ventilation ($p < 0.001$) were associated with increased mortality, as was development of a pneumothorax ($p < 0.001$). Factors that were not associated with mortality included gender, race, tobacco use, haematocrit, new diagnosis of HIV, first versus repeat episode of PCP, and use of PCP prophylaxis or CART before admission.

In multivariate analysis using stepwise regression, the best fitting model retained six predictors that were associated with mortality (table 3). Significant predictors included two socio-demographic variables and three laboratory variables: age (adjusted odds ratio (AOR) per 10-year increase, 1.69; 95% CI 1.08 to 2.65; $p = 0.02$); recent injection drug use (AOR 2.86; 95% CI 1.28 to 6.42; $p = 0.01$); total bilirubin > 0.6 mg/dl (AOR 2.59; 95% CI 1.19 to 5.62; $p = 0.02$); serum albumin < 3 g/dl (AOR 3.63; 95% CI 1.72 to 7.66; $p = 0.001$); and A–a O_2 gradient ≥ 50 mm Hg (AOR 3.02; 95% CI 1.41 to 6.47; $p = 0.004$). CD4 count < 50 cells/ μ l was retained in the best-fitting model but was not a significant predictor of mortality (AOR 2.34; 95% CI 0.95 to 5.80; $p = 0.07$).

A prediction rule for PCP mortality

Based on the multivariate analysis results, we stratified patients by increasing risk for mortality using two prediction rules, both of which assigned one point for each predictor present. In the first rule, all five independent predictors from multivariate analysis were used to stratify patients by increasing mortality, resulting in a 6-point score (range 0–5). Mortality ranged from 4% (score 0 or 1) to 48% (score 4 or 5, fig 1). A simpler model

based on three variables—age, A–a O_2 gradient and serum albumin, resulted in a 4-point score (range 0–3) and stratified patients into groups with 0% mortality (score 0) to 41% (score 3, fig 2). The sensitivities, specificities, and positive and negative predictive values are given in table 4 and fig 3. While the 4-point score is simpler to use and requires less clinical information, model testing by the quasi-log-likelihood information criterion (QIC) indicated that the 6-point score was a better fit (6-point and 4-point QIC scores 232.3 and 241.9, respectively). The 4-point score also classified fewer patients than the full 6-point score into combined high and low mortality groups (109 vs 167 patients, 28% vs 46% of total patients, respectively).

DISCUSSION

In this single-centre study of 524 HIV-infected patients with laboratory-diagnosed PCP during the CART era, we found an overall mortality of 10.3% and identified five independent and objective predictors of mortality that are readily available at illness presentation. Using these predictors, we then developed two prediction rules that stratify patients by mortality risk upon presentation to medical care.

The overall mortality of 10.3% in our study cohort is within the range of mortality rates, 7–13%, reported in large cohorts (> 500 subjects) of HIV-infected patients with PCP from the pre-CART and early CART eras,^{9 11 20 25} suggesting that mortality from PCP has not changed in the current era. Other studies, however, have documented a trend toward decreased PCP mortality in the CART era even in patients who were not receiving CART,¹⁸ a finding that has been attributed to improvements in ICU care.^{26–28} While the number of PCP cases per year has declined at our institution, those persons still presenting with PCP are rarely receiving antiretroviral therapy or PCP prophylaxis and still have an appreciable, and possibly unchanged, mortality.

We identified five significant and objective predictors of mortality that are readily available at illness presentation. Except for the A–a O_2 gradient, none of the significant predictors of mortality identified in multivariate analysis was strictly associated with the severity of underlying HIV disease or respiratory compromise from PCP. Instead, our results suggest that non-HIV-associated factors that reflect the presence of underlying medical co-morbidities and general severity of illness, namely age, injection drug use, serum total bilirubin and serum albumin, may be more accurate predictors of mortality from PCP than HIV-associated factors, such as CD4 cell count or history of opportunistic infection. Age is a predictor that is widely used in risk stratification rules for community-acquired pneumonia, and correlates with the number of medical co-morbidities in HIV-infected patients.^{29–30} In addition, many studies have reported age and serum albumin as predictors of mortality not only for patients with PCP but also for HIV-infected patients requiring intensive care.^{12 18–20 31} To our knowledge, the associations between recent injection drug use and serum total bilirubin with increased PCP mortality have not been reported. Recent injection drug use increases the presence of concurrent medical co-morbidities and reflects the absence of appropriate, preventive medical care. Previous studies have either had a low prevalence of injection drug users or evaluated the association between any history of injection drug use and PCP mortality, which would include persons who had quit years previously.^{18 20} The serum bilirubin has been used in validated scoring systems (eg, Simplified Acute Physiology Score II, Pneumonia Severity Index) to assess severity of illness and predict mortality in patients with critical illness and pneumonia.^{30 32} As a

Table 2 Characteristics associated with mortality in bivariate analysis in 524 HIV-infected patients with PCP

	Died* (n = 54)	Survived (n = 470)	Bivariate, unadjusted RR (95% CI)	p Value
Sociodemographic				
Mean age, per 10-year increase	43.6 (8.4)	40.3 (7.9)	1.64 (1.15 to 2.36)	0.01
Gender				
Male	44 (10)	412 (90)	0.60 (0.27 to 1.30)	0.19
Female	10 (15)	58 (85)		
Race				
Black	10 (7)	143 (93)	0.52 (0.25 to 1.07)	0.08
Non-black	44 (12)	327 (88)		
Tobacco use				
Yes	41 (12)	306 (88)	1.61 (0.82 to 3.17)	0.17
No	12 (8)	145 (92)		
Recent injection drug use†				
Yes	17 (18)	78 (82)	2.21 (1.19 to 4.10)	0.01
No	37 (9)	374 (91)		
Homeless				
Yes	4 (6)	68 (94)	0.46 (0.16 to 1.30)	0.14
No	50 (11)	386 (89)		
Medical history				
New diagnosis of HIV				
Yes	9 (7)	112 (93)	0.63 (0.30 to 1.33)	0.23
No	45 (11)	356 (89)		
Medical co-morbidity‡				
Yes	37 (13)	256 (87)	1.84 (1.01 to 3.33)	0.04
No	17 (7)	214 (93)		
History of PCP				
Yes	14 (10)	124 (90)	1.00 (0.53 to 1.87)	0.99
No	40 (10)	346 (90)		
History of KS				
Yes	5 (16)	26 (84)	1.74 (0.65 to 4.66)	0.27
No	49 (10)	444 (90)		
Pulmonary KS at admission				
Yes	2 (20)	8 (80)	1.88 (0.37 to 9.41)	0.44
No	19 (12)	143 (88)		
Renal failure				
Yes	6 (12)	46 (88)	1.13 (0.47 to 2.75)	0.78
No	48 (10)	419 (90)		
Hepatic insufficiency				
Yes	27 (23)	91 (77)	2.27 (1.17 to 4.38)	0.02
No	17 (11)	133 (89)		
CART prior to admission				
Yes	6 (10)	52 (90)	0.99 (0.41 to 2.40)	0.98
No	48 (10)	410 (90)		
PCP prophylaxis				
Yes	11 (15)	64 (85)	1.60 (0.78 to 3.24)	0.20
No	43 (10)	397 (90)		
Vital signs				
Mean temperature, per 0.5°C increase	38.1 (1)	38.6 (1)	0.79 (0.68 to 0.92)	0.002
Mean pulse, per 10 beats/min increase	111 (18)	107 (18)	1.13 (0.97 to 1.30)	0.12
Mean systolic blood pressure, per 10 mm Hg increase	103 (15)	108 (15)	0.78 (0.63 to 0.96)	0.02
Respiratory rate				
>22 breaths/min	30 (13)	208 (87)	1.38 (0.79 to 2.43)	0.26
≤22 breaths/min	24 (9)	230 (91)		
Room air O ₂ saturation				
<90%	33 (19)	145 (81)	3.29 (1.82 to 5.94)	<0.001
≥90%	19 (6)	278 (94)		
Laboratory values				
CD4 cell count				
<50 cells/μl	42 (12)	304 (88)	2.23 (1.09 to 4.56)	0.03
≥50 cells/μl	10 (6)	159 (94)		
HIV viral load				
>12 log copies/ml	27 (10)	233 (90)	1.06 (0.59 to 1.91)	0.85
≤12 log copies/ml	23 (10)	209 (90)		

Continued

Table 2 Continued

	Died* (n = 54)	Survived (n = 470)	Bivariate, unadjusted RR (95% CI)	p Value
Total lymphocyte count				
>0.7 × 10 ⁹ /l	20 (8)	246 (92)	0.51 (0.28 to 0.91)	0.02
≤ 0.7 × 10 ⁹ /l	32 (13)	206 (87)		
Mean haematocrit, per 1% increase	33.8 (6.2)	34.9 (5.4)	0.96 (0.91 to 1.02)	0.19
Normal sodium values§				
Yes	21 (7)	272 (93)	0.45 (0.25 to 0.80)	0.01
No	33 (15)	193 (85)		
BUN				
>13 mg/dl	38 (16)	194 (84)	3.21 (1.74 to 5.94)	<0.001
≤ 13 mg/dl	16 (6)	264 (94)		
Total bilirubin				
>0.6 mg/dl	33 (18)	152 (82)	2.86 (1.59 to 5.14)	<0.001
≤ 0.6 mg/dl	20 (7)	265 (93)		
Albumin				
<3 g/dl	32 (17)	151 (83)	3.28 (1.77 to 6.10)	<0.001
≥ 3 g/dl	17 (6)	264 (94)		
A-a O ₂ gradient				
≥ 50 mm Hg	36 (19)	153 (81)	4.14 (2.13 to 8.05)	<0.001
< 50 mm Hg	13 (5)	229 (95)		
LDH				
>360 U/l	31 (13)	203 (87)	1.92 (1.04 to 3.56)	0.04
≤ 360 U/l	18 (7)	225 (93)		
Complication				
Pneumothorax at admission				
Yes	2 (67)	1 (33)	17.4 (1.61 to 186.9)	0.02
No	52 (10)	446 (90)		

*Values are shown as number (%) unless otherwise stated; means are presented with the SD.

†Recent injection drug use is defined as drug use during the 6 months before admission.

‡Medical co-morbidity is defined as having a history of opportunistic infection, renal failure (creatinine >1.2 mg/dl) or hepatic insufficiency (INR ≥ 1.2).

§Normal sodium is defined as a value between 136 and 144 mmol/l.

A-a O₂ gradient, alveolar-arterial oxygen gradient; BUN, blood urea nitrogen; CART, combination antiretroviral therapy; INR, international normalised ratio; KS, Kaposi sarcoma; LDH, lactate dehydrogenase; PCP, *Pneumocystis pneumonia*.

reflection of end-organ dysfunction, bilirubin may also be a marker of sepsis or septic shock, and has recently been reported to predict development of acute respiratory distress syndrome and mortality in patients with sepsis.³³

Both mortality prediction rules we present have distinct advantages. The three-predictor rule is easier to use and requires fewer clinical data, but classified fewer patients into groups with extremely high or low mortality compared with the five-predictor

Table 3 Characteristics associated with mortality in multivariate analysis in 524 HIV-infected patients with PCP

	Died* (n = 54)	Survived (n = 470)	Bivariate, unadjusted RR (95% CI), p value	Multivariate, adjusted OR (95% CI), p value†
Mean age, per 10-year increase	43.6 (8.4)	40.3 (7.9)	1.64 (1.15 to 2.36), 0.01	1.69 (1.08 to 2.65), 0.02
Recent injection drug use‡				
Yes	17 (18)	78 (82)	2.21 (1.19 to 4.10), 0.01	2.86 (1.28 to 6.42), 0.01
No	37 (9)	374 (91)		
CD4 cell count				
<50 cells/μl	42 (12)	304 (88)	2.23 (1.09 to 4.56), 0.03	2.34 (0.95 to 5.80), 0.07
≥ 50 cells/μl	10 (6)	159 (94)		
Total bilirubin				
>0.6 mg/dl	33 (18)	152 (82)	2.86 (1.59 to 5.14), <0.001	2.59 (1.19 to 5.62), 0.02
≤ 0.6 mg/dl	20 (7)	265 (93)		
Albumin				
<3 g/dl	32 (17)	151 (83)	3.28 (1.77 to 6.10), <0.001	3.63 (1.72 to 7.66), 0.001
≥ 3 g/dl	17 (6)	264 (94)		
A-a O ₂ gradient				
≥ 50 mm Hg	36 (19)	153 (81)	4.14 (2.13 to 8.05), <0.001	3.02 (1.41 to 6.47), 0.004
< 50 mm Hg	13 (5)	229 (95)		

*Values are shown as number (%) unless otherwise stated; means are presented with the SD.

†Forty-three deaths in 358 observations retained in the multivariate model.

‡Recent injection drug use is defined as drug use during the 6 months before admission.

PCP, *Pneumocystis pneumonia*; A-a O₂ gradient, alveolar-arterial oxygen gradient.

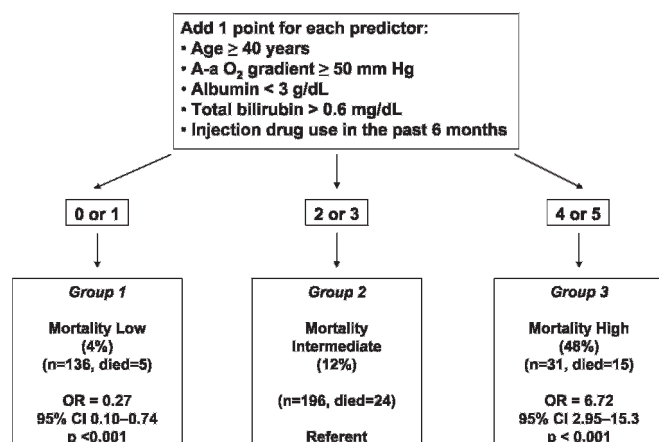


Figure 1 Stratifying patients with HIV-associated *Pneumocystis* pneumonia by mortality at illness presentation using all five predictors identified in multivariate analysis.

rule. Although the sensitivities and specificities of the two prediction rules were comparable, model testing using QIC scores showed that the five-predictor rule had a better fit. Two previous studies from the pre-CART and early CART eras have described strategies to predict mortality from PCP. One prediction model incorporated the A–a O₂ gradient, total lymphocyte count and body mass index,⁹ while the other used HIV wasting, the A–a O₂ gradient and serum albumin.²⁰ However, both studies included patients who had presumptive PCP without microbiological confirmation. In addition, HIV wasting is subject to variability in provider categorisation and varying clinical manifestations, as noted by the study's authors.^{20–34} In contrast, our mortality prediction rules are based on objective clinical and laboratory characteristics which are widely available and easily assessed in most HIV-infected patients presenting with PCP in high-income countries. Because our goal was to provide a simple, clinically useful prediction rule to identify patients at presentation with the highest and lowest risk for mortality, the algorithm has limited ability to stratify further patients with an intermediate mortality risk (Group 2, figs 1 and 2). At institutions where the risk of loss to follow-up is low, it is possible that persons who are predicted to

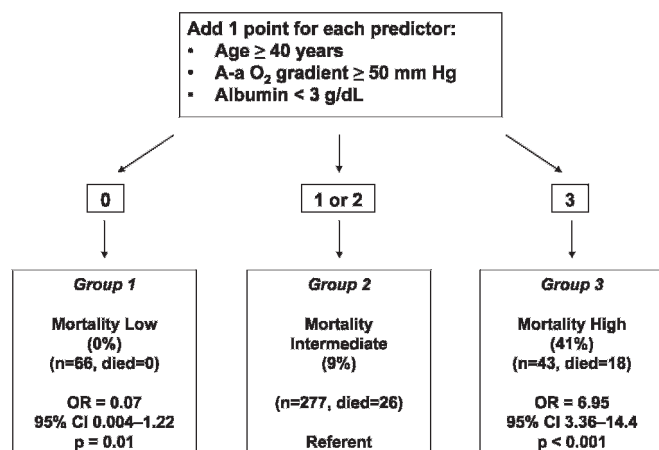


Figure 2 Stratifying patients with HIV-associated *Pneumocystis* pneumonia by mortality at illness presentation using three predictors—age, serum albumin and alveolar–arterial oxygen gradient (A–a O₂ gradient)—identified in multivariate analysis.

Table 4 Test characteristics of mortality prediction rules for HIV-associated PCP

Rule	Number of risk factors (n = 363)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Five predictors*	>0	100	0	12.1	NA
	>1	100	12.5	13.6	100
	>2	88.6	41.1	17.2	96.3
	>3	63.6	75.2	26.2	93.8
	>4	34.1	95.0	48.4	91.3
	>5	11.4	100	100	89.1
Three predictors†	>0	100.0	0.0	12.1	NA
	>1	100.0	19.7	14.7	100
	>2	63.6	62.4	18.9	92.6
	>3	40.9	93.4	46.2	92.0

*Predictors are age, alveolar–arterial oxygen gradient (A–a O₂ gradient), albumin, total bilirubin and recent injection drug use.

†Predictors are age, A–a O₂ gradient and albumin.

NPV, negative predictive value; PCP, *Pneumocystis* pneumonia; PPV, positive predictive value.

have a low risk for mortality may not require admission for diagnosis and treatment. Similarly, persons who are predicted to have a high risk for mortality may warrant closer observation, such as on a “step-down” unit or in the ICU. Further research is needed to validate the predictive accuracy of our algorithm in patient cohorts from other institutions.

In addition to the limitations discussed above, our study's main drawback is that it reflects the experience and patient population at a single public hospital in the USA and may not be more broadly applicable to all HIV-infected patients with PCP. Earlier studies have documented variations in patient demographics and processes of care among HIV-infected patients with PCP based on hospital type (ie, Veterans Affairs, public or private),³⁵ and the high prevalence of injection drug use and sensitivity of sputum induction for PCP diagnosis in our study may make our findings less generalisable to other institutions. Our centre's reliance on sputum induction rather than bronchoscopy for PCP diagnosis may explain why we did not identify pulmonary KS as a predictor of mortality, in contrast to findings reported by Walzer and colleagues at a centre that predominantly performs bronchoscopy for PCP diagnosis.¹⁸ We hope that our prediction rules will be validated using large cohorts of HIV-infected patients with PCP at other institutions, as has been recently described.^{17–18} Nevertheless, while sociodemographic characteristics, severity of illness and clinical practices may differ across patient cohorts and institutions, we

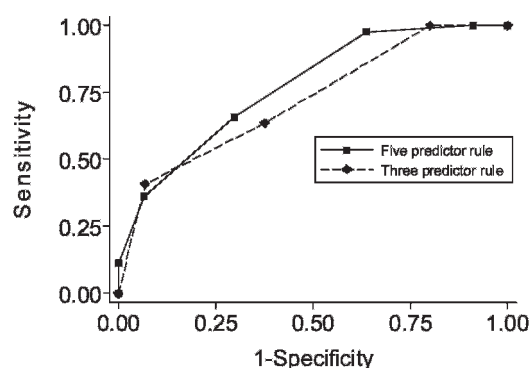


Figure 3 Receiver operating curves for the five-predictor and three-predictor PCP mortality prediction rules.

believe that there is a biological basis and clinical rationale for the variables we identified to stratify patients by mortality. These are predictors which reflect presence of medical co-morbidity, severity of pulmonary disease and overall health status, and should be broadly applicable to most HIV-infected patients with PCP.

In conclusion, we found that mortality from HIV-associated PCP in the CART era remains unchanged from studies performed earlier in the HIV/AIDS epidemic. Using clinical and laboratory data routinely obtained at the time of presentation, we developed two mortality prediction rules that stratify patients by risk for in-hospital mortality. While our prediction rules require further validation in cohorts from different institutions, they are potentially a practical method of identifying patients who are at high and low risk for death early in the hospital course, and therefore may assist clinicians in assessing severity of illness and more accurately deciding on management strategies.

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REFERENCES

1. **Pallela FJ Jr**, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;**338**:853–60.
2. **Kaplan JE**, Hanson D, Dworkin MS, *et al.* Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000;**30**(Suppl 1):S5–14.
3. **Morris A**, Lundgren JD, Masur H, *et al.* Current epidemiology of *Pneumocystis pneumonia*. *Emerg Infect Dis* 2004;**10**:1713–20.
4. **Kales CP**, Murren JR, Torres RA, *et al.* Early predictors of in-hospital mortality for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. *Arch Intern Med* 1987;**147**:1413–7.
5. **Benson CA**, Spear J, Hines D, *et al.* Combined APACHE II score and serum lactate dehydrogenase as predictors of in-hospital mortality caused by first episode *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. *Am Rev Respir Dis* 1991;**144**:319–23.
6. **Brenner M**, Ognibene FP, Lack EE, *et al.* Prognostic factors and life expectancy of patients with acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis* 1987;**136**:1199–206.
7. **Zaman MK**, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis* 1988;**137**:796–800.
8. **Speich R**, Weber R, Kronauer CM, *et al.* Prognostic score for *Pneumocystis carinii* pneumonia. *Respiration* 1990;**57**:259–63.
9. **Bennett CL**, Weinstein RA, Shapiro MF, *et al.* A rapid preadmission method for predicting inpatient course of disease for patients with HIV-related *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med* 1994;**150**:1503–7.
10. **De Palo VA**, Millstein BH, Mayo PH, *et al.* Outcome of intensive care in patients with HIV infection. *Chest* 1995;**107**:506–10.
11. **Hawley PH**, Ronco JJ, Guillemi SA, *et al.* Decreasing frequency but worsening mortality of acute respiratory failure secondary to AIDS-related *Pneumocystis carinii* pneumonia. *Chest* 1994;**106**:1456–9.
12. **Wachter RM**, Russi MB, Bloch DA, *et al.* *Pneumocystis carinii* pneumonia and respiratory failure in AIDS. Improved outcomes and increased use of intensive care units. *Am Rev Respir Dis* 1991;**143**:251–6.
13. **Bedos JP**, Dumoulin JL, Gachot B, *et al.* *Pneumocystis carinii* pneumonia requiring intensive care management: survival and prognostic study in 110 patients with human immunodeficiency virus. *Crit Care Med* 1999;**27**:1109–15.
14. **Peruzzi WT**, Skoutelis A, Shapiro BA, *et al.* Intensive care unit patients with acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia: suggested predictors of hospital outcome. *Crit Care Med* 1991;**19**:892–900.
15. **Wachter RM**, Luce JM, Turner J, *et al.* Intensive care of patients with the acquired immunodeficiency syndrome. Outcome and changing patterns of utilization. *Am Rev Respir Dis* 1986;**134**:891–6.
16. **Rosen MJ**, Cucco RA, Teirstein AS. Outcome of intensive care in patients with the acquired immunodeficiency syndrome. *J Intensive Care Med* 1986;**1**:55–60.
17. **Radhi S**, Alexander T, Ukwu M, *et al.* Outcome of HIV-associated *Pneumocystis pneumonia* in hospitalized patients from 2000 through 2003. *BMC Infect Dis* 2008;**8**:118.
18. **Walzer PD**, Evans HE, Copas AJ, *et al.* Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985–2006. *Clin Infect Dis* 2008;**46**:625–33.
19. **Benfield TL**, Helweg-Larsen J, Bang D, *et al.* Prognostic markers of short-term mortality in AIDS-associated *Pneumocystis carinii* pneumonia. *Chest* 2001;**119**:844–51.
20. **Arozullah AM**, Yarnold PR, Weinstein RA, *et al.* A new preadmission staging system for predicting inpatient mortality from HIV-associated *Pneumocystis carinii* pneumonia in the early highly active antiretroviral therapy (HAART) era. *Am J Respir Crit Care Med* 2000;**161**:1081–6.
21. **Azoulay E**, Parrot A, Flahault A, *et al.* AIDS-related *Pneumocystis carinii* pneumonia in the era of adjunctive steroids: implication of BAL neutrophilia. *Am J Respir Crit Care Med* 1999;**160**:493–9.
22. **Curtis JR**, Yarnold PR, Schwartz DN, *et al.* Improvements in outcomes of acute respiratory failure for patients with human immunodeficiency virus-related *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med* 2000;**162**:393–8.
23. **Huang L**, Hecht FM, Stansell JD, *et al.* Suspected *Pneumocystis carinii* pneumonia with a negative induced sputum examination. Is early bronchoscopy useful? *Am J Respir Crit Care Med* 1995;**151**:1866–71.
24. **Rosner B.** *Fundamentals of Biostatistics*. 4th edn. New York: Duxbury Press, 1995.
25. **Kelley CF**, Checkley W, Mannino DM, *et al.* Trends in hospitalizations for AIDS-associated *Pneumocystis jirovecii* pneumonia in the United States (1986–2005). *Chest* 2009;**136**:190–7.
26. **Miller RF**, Allen E, Copas A, *et al.* Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. *Thorax* 2006;**61**:716–21.
27. **Davis JL**, Morris A, Kallet RH, *et al.* Low tidal volume ventilation is associated with reduced mortality in HIV-infected patients with acute lung injury. *Thorax* 2008;**63**:988–93.
28. **Travis J**, Hart E, Helm J, *et al.* Retrospective review of *Pneumocystis jirovecii* pneumonia over two decades. *Int J STD AIDS* 2009;**20**:200–1.
29. **Goulet JL**, Fultz SL, Rimland D, *et al.* Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity? *Clin Infect Dis* 2007;**45**:1593–601.
30. **Fine MJ**, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;**336**:243–50.
31. **Morris A**, Wachter RM, Luce J, *et al.* Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS* 2003;**17**:73–80.
32. **Le Gall JR**, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993;**270**:2957–63.
33. **Zhai R**, Sheu CC, Su L, *et al.* Serum bilirubin levels on ICU admission are associated with ARDS development and mortality in sepsis. *Thorax* 2009;**64**:784–90.
34. **Corcoran C**, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1999;**340**:1740–50.
35. **Uphold CR**, Deloria-Knoll M, Pallela FJ Jr, *et al.* US hospital care for patients with HIV infection and pneumonia: the role of public, private, and Veterans Affairs hospitals in the early highly active antiretroviral therapy era. *Chest* 2004;**125**:548–56.