

Outcomes of patients admitted to the intensive care unit with idiopathic pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a progressive and usually fatal disease of unknown aetiology, characterised by sequential acute lung injury with subsequent scarring and end-stage lung disease.^{1,2} In most patients, the course of the disease is progressive, with episodes of acute deterioration, the exact nature of which is usually undefined.^{3,4} Median survival of patients with IPF has been reported to range from 3 to 5 years.^{5,6} Current therapy includes corticosteroids and cytotoxic agents, but these appear to improve neither survival nor quality of life.^{1,7} For patients admitted to an ICU with an acute exacerbation of IPF^{3,8} or intercurrent illness, the requirement for mechanical ventilation is high, and the recorded mortality is substantial at 73%–100%.^{9–13} Patients with advanced IPF have significantly deranged lung mechanics, with a decrease in static and dynamic compliance and marked increase in resistance of the respiratory system.¹⁴ The benefit of mechanical ventilation in relieving hypoxaemia under such circumstances is not clear.¹⁵

This study aimed to evaluate the outcome and role of ICU admission in patients with a diagnosis of IPF who presented with acute respiratory deterioration.

Methods

Patient selection

A computer register of patients admitted to the ICU at the Queen Elizabeth Hospital (QEH) was used. All patients with an established diagnosis of IPF who were admitted to the ICU with acute respiratory failure between January 1996 and December 2006 were studied retrospectively. The diagnosis of IPF was confirmed using criteria based on modified American Thoracic Society guidelines,^{9,12} suitable for retrospective studies.

Major criteria were:

- exclusion of other known causes of interstitial lung disease, such as drug toxicities, environmental agents and connective tissue diseases;
- abnormal pulmonary function test results, showing a restrictive pattern (reduced vital capacity, often with an increased ratio of forced expiratory volume in 1 s to forced vital capacity [FEV_{1,0}/FVC]);
- high-resolution computed tomography (CT) evidence of pulmonary fibrosis, characterised by irregular septal thick-

ABSTRACT

Objective: To evaluate outcomes of patients admitted to an intensive care unit with idiopathic pulmonary fibrosis (IPF) and acute respiratory deterioration.

Design: Retrospective cohort study.

Setting: University-affiliated, tertiary adult ICU.

Participants: All patients admitted to the ICU between January 1996 and December 2006 with an established diagnosis of IPF were identified from review of case notes, ICU charts and electronic hospital records. Patient demographics, ICU investigation and treatment profiles were characterised; final follow-up was electronically from the State Registry.

Main outcome measures: Primary study end-point was survival from ICU admission until December 2007; secondary end-points were survival from diagnosis and from first respiratory hospital admission.

Results: 24 patients were identified with IPF, diagnosed by lung biopsy (8) and by clinical criteria; 21 patients were admitted with acute respiratory failure, and three postoperatively. Mean age was 66 (SD, 16) years, mean APACHE III score was 82 (SD, 37), and 14 were men. Admission diagnoses were acute exacerbation of IPF (8), pneumonia (10), acute heart failure (3) and postoperative (3). All patients received broad-spectrum antibiotics, and 17 continued to receive corticosteroids prescribed previously. Nineteen patients were mechanically ventilated for a mean of 19.1 days (SD, 25.3); 13 of 19 patients had non-invasive ventilation before mechanical ventilation, and four received only non-invasive ventilation. Sixteen mechanically ventilated patients died in the ICU, another six died in hospital (2–30 days after ICU discharge); and two were discharged home. Median survival (95% CI) was 16 (9–19) days from ICU admission; 55 (18–284) days from first respiratory admission; and 1.05 (0.34–1.75) years from IPF diagnosis.

Conclusions: Outcomes of patients with IPF admitted to the ICU are poor. Indications for mechanical ventilation appear uncertain.

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ening, traction bronchiectasis and subpleural honeycombing; and

- transbronchial lung biopsy or bronchoalveolar lavage showing no features that supported an alternative diagnosis.

Minor criteria were:

- age over 50 years;
- insidious onset of otherwise unexplained dyspnoea on exertion;
- duration of illness of 3 months or longer; and
- bi-basal inspiratory crackles.

In the absence of results of a transbronchial lung biopsy, patients fulfilling high-resolution CT criteria for pulmonary fibrosis along with any three of the four minor criteria were included in the study.

Acute exacerbation of IPF was defined by the following criteria:

- exacerbation of dyspnoea within 4–8 weeks;
- development of acute respiratory failure;
- absence of apparent infectious agents and, if lung biopsy results were available, a superimposed histological pattern of diffuse alveolar damage; and
- ICU admission for further support and management.^{3,8}

Exclusion criteria included:

- evidence of concurrent or past connective tissue disorders;
- presence of infection in the first 5 days of ICU admission;
- evidence of severe left ventricular dysfunction documented as an ejection fraction less than 30%;
- significant history of occupational exposure; and
- presence of irreversible systemic disease such as end-stage neoplasm.

Data collection

The following data were abstracted from the case notes and ICU flow charts: demographics; duration of diagnosis before ICU admission; date of first respiratory admission (related to the diagnosis of IPF) at QEH, clinical features (bi-basal end-inspiratory crackles), investigations (chest radiography, CT and lung biopsy results), and treatment measures (corticosteroid, immunosuppressive or antibiotic therapy); Acute Physiology and Chronic Health Evaluation III (APACHE III) score,¹⁶ use of non-invasive and invasive mechanical ventilation, P_{aO_2}/F_{iO_2} ratios and positive end-expiratory pressure (PEEP) levels. The most recent results of pulmonary function tests, subsequent to the diagnosis of IPF and performed within 1 year of the current (ICU) hospitalisation were recorded. Arterial blood gas analyses showing the P_{aO_2}/F_{iO_2} ratio on ICU admission were accessed from ICU flow charts. Reports of extensive surveillance cultures (including sputum, blood and urine cultures) and serology tests were recorded from the case notes and confirmed by cross-checking with the hospital electronic pathology systems.

Table 1. Baseline characteristics of 24 patients admitted to the ICU with idiopathic pulmonary fibrosis

Patient characteristic	
Duration, median (range)	
First respiratory admission to ICU admission (days) (<i>n</i> = 24)*	3.5 (0.1–3861)
Diagnosis to ICU admission (years) (<i>n</i> = 21) [†]	0.82 (0.03–10.25)
Pulmonary function, mean (SD)	
Vital capacity (L) (<i>n</i> = 14)	2.13 (0.94)
FEV _{1,0} /FVC (%) (<i>n</i> = 14)	87 (11.9)
Total lung capacity (L) (<i>n</i> = 9)	3.87 (1.46)
Residual volume (L) (<i>n</i> = 8)	1.39 (0.37)
DLCO (mL/min/mmHg) [†]	8.4 (1.63)
Number of patients with	
HRCT suggestive of pulmonary fibrosis	24/24
Lung biopsy	8/24
Corticosteroid therapy	17/24
Immunosuppressive therapy	4/24
Domiciliary oxygen	9/24

HRCT = high-resolution computed tomography results.

FEV_{1,0}/FVC = ratio of forced expiratory volume in 1 s to forced vital capacity.

DLCO = diffusing capacity of lung (reference range at rest, 25 mL/min/mmHg).

* In three patients, the first respiratory admission coincided with the index ICU admission.

[†] Date of diagnosis could not be established exactly in three patients.

Outcome measures

The primary end-point was survival from ICU admission. Secondary end-points were survival from date of first respiratory admission (related to the diagnosis of IPF) at QEH, and survival from initial (respiratory) diagnosis. Long-term survival of patients discharged from hospital, to December 2007, was identified electronically from the South Australian State Births and Deaths Registry.

Approval for the conduct of the study was granted by the QEH Ethics of Research Committee.

Statistical analysis

Continuous variables were expressed as mean (SD) or median (range). Survival over time was characterised by Kaplan–Meier and Cox model estimates.¹⁷ Cox model fit was assessed by approximation of cumulative Cox–Snell residuals to (–log) Kaplan–Meier estimates, residual plots and specific testing of the proportional hazards assumption, and by Harrell’s C-statistic and “added-variable” goodness-of-fit tests.¹⁸ As the dataset was small, it was expected that only one or two variables would be incorporated into the Cox model(s).¹⁹ Non-linearity of predictor effect was

checked via residual analysis and modelled using cubic (degree = 3) splines, as implemented in the user-written Stata module "mvs".^{20,21} Splines are flexible functions created by joining polynomials of the same degree at particular x values (knots), and are continuous ("smooth") at these knots; in the mvs formulation, the cubic regression spline is restricted to linearity beyond two boundary knots. As the cubic spline is a continuous smooth function, the coefficient effects at the knots are not subject to literal effect interpretation (compared with other coefficients) and are not quoted.

Stata version 10 statistical software (Stata Corp, College Station, Tex, 2007) was used. Statistical significance was set at $P \leq 0.05$.

Results

Demographics

Twenty-four patients admitted to the ICU fulfilled the criteria for IPF over the 11-year period 1996–2006, during which time 5864 other patients were also admitted to the ICU. The baseline characteristics of patients with IPF are shown in Table 1; mean age was 66 (SD, 16) years, and they included 14 men. Few underwent formal pulmonary function tests other than FEV_{1,0} and FVC. Four had been prescribed immunosuppressive therapy: a combination of corticosteroids and azathioprine (plus domiciliary oxygen) in three, and a trial drug (everolimus) in one.

ICU course

Patients were admitted to the ICU at a median of 1.05 years after diagnosis (range, 0.03–11.4 years). Admission diagnoses were acute exacerbation of IPF (8), pneumonia (10), heart failure (evidenced by echocardiography, 3) and post-operative (after acute gastrointestinal surgery, 2; and thoracotomy for empyema, 1). Most patients had an elevated total white cell count and C-reactive protein level (Table 2). Microbiological testing of sputum showed a pathogen in 10 patients; serological tests were negative for atypical organisms (*Legionella*, *Chlamydia*, *Mycoplasma* and respiratory viruses) in 22 patients (Table 3). Bronchoalveolar lavage was performed in six of the 24 patients while they were in the ICU, and was positive for a microorganism in three (*Candida albicans*, *Aspergillus fumigatus*, and *Nocardia asteroides* with *C. albicans*, respectively); the latter two patients were receiving corticosteroids. Echocardiography was performed in 14 patients: three had evidence of heart failure (left ventricular failure in two, and right heart failure in the other, with estimated right ventricular systolic pressure of 56 mmHg); six patients had abnormalities consistent with pulmonary artery hypertension; and five had no recorded dysfunction.

Table 2. Clinical status of 24 patients in the ICU

Variable	Mean (SD) or no.*
Admission PaO ₂ /FIO ₂	96 (48)
APACHE III score	82 (37)
Lowest PEEP (cmH ₂ O)	6 (2.6)
Highest PEEP (cmH ₂ O)	11 (3.5)
High white cell count (> 12.0 × 10 ⁹ /L)	23/24
High C-reactive protein level (> 10 mg/L)	11/15
Intubation and mechanical ventilation	19/24
Duration of ventilation (h) [†]	494 (597)
Median (range)	282 (8.8–2465)
Non-invasive mechanical ventilation, exclusively	4/24
Duration of non-invasive ventilation (h)	317 (325)
Median (range)	264 (22–772)
ICU length of stay (days)	15.8 (21.2)
Median (range)	10 (0.1–103)
Death in hospital	22/24

APACHE = Acute Physiology And Chronic Health Evaluation.

PEEP = positive end-expiratory pressure.

* Unless otherwise specified. † Duration of ventilation represents total hours of non-invasive and invasive mechanical ventilation.

Table 3. Admission diagnosis and cause of death in 24 patients with IPF

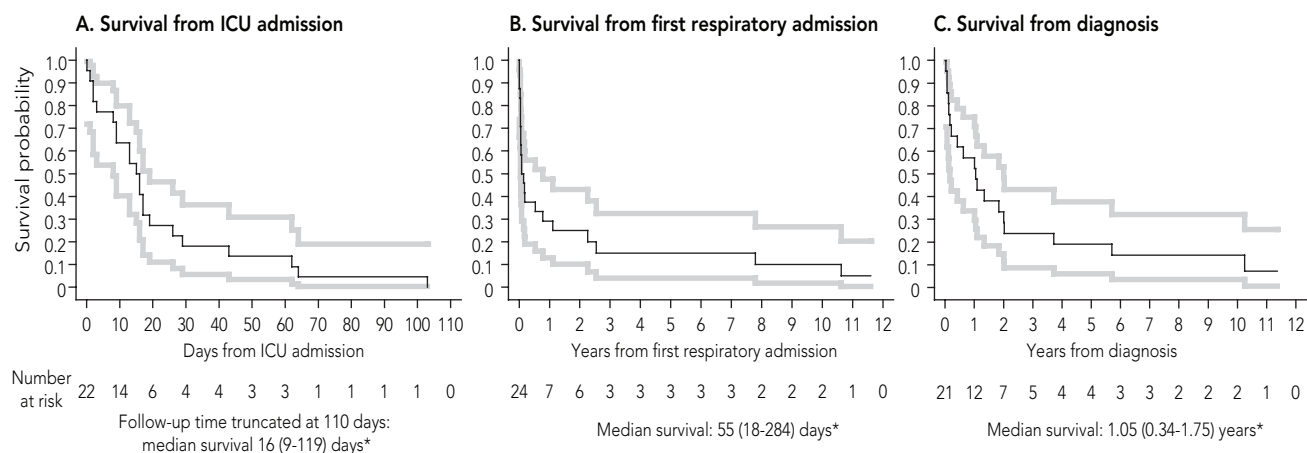
Admission diagnosis	No. of patients	No. who died (cause of death)
Pneumonia	10 (42%)	10 (6 MOF, 4 RH)
<i>Pseudomonas</i> sp.	2	
MRSA	2	
<i>Pseudomonas</i> sp. + MRSA	1	
<i>Candida albicans</i>	2	
<i>Aspergillus fumigatus</i>	1	
<i>Nocardia asteroides</i> + <i>C. albicans</i>	1	
<i>Klebsiella oxytoca</i>	1	
Acute exacerbation of IPF	8 (33%)	8 (RH)
Cardiac failure	3 (13%)	2 (1 MOF, 1 RH)
Emergency surgery	2 (8%)	1 (RH)
Elective surgery	1 (4%)	1 (RH)

IPF = idiopathic pulmonary fibrosis.

MOF = multiorgan failure. RH = refractory hypoxaemia.

MRSA = methicillin-resistant *Staphylococcus aureus*.

During the ICU stay, all patients received a course of antibiotics determined by the treating intensive care physician. Seventeen patients who had been prescribed corticosteroid therapy before admission continued to receive

Figure 1. Kaplan–Meier survival curves with 95% CI for primary and secondary outcomes

A: For survival from ICU admission, the follow-up time was truncated at 110 days, and the two long-term survivors were not included in the “number at risk”.

B: For survival from date of first respiratory admission at Queen Elizabeth Hospital (related to the diagnosis of idiopathic pulmonary fibrosis); the first respiratory admission coincided with the index ICU admission in three patients.

C: For survival from diagnosis, the date of diagnosis could not be established exactly in three patients.

* Median (95% CI) survival.

corticosteroids in the ICU (150–200 mg hydrocortisone per day); the remaining seven who had not been prescribed corticosteroids did not receive them in the ICU. None of the patients received high-dose pulse therapy with methylprednisolone.

On ICU admission, all patients had severe hypoxaemia (Table 2). Nineteen patients were intubated and mechanically ventilated; in 13, this followed a trial of non-invasive ventilation. Four received non-invasive ventilation only, and the other received supplemental oxygen by mask.

Sixteen patients died in the ICU while receiving mechanical ventilation, and six died in hospital (at 2–30 days after ICU discharge). The overall ICU mortality was 67%, and hospital mortality was 92%. The cause of death was refractory hypoxaemia in 15 patients and multiorgan failure in seven (Table 3). Two patients, neither of whom received mechanical ventilation in the ICU, survived to be discharged home.

Survival analyses

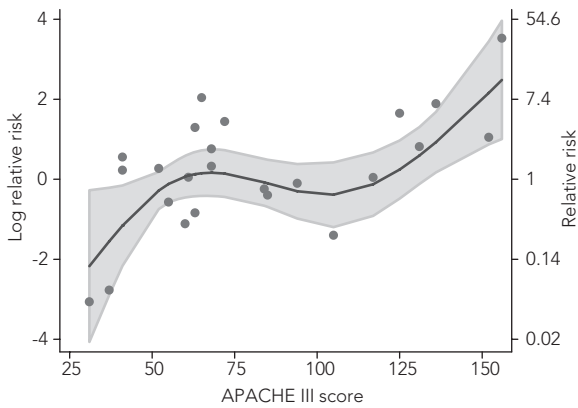
Median survival of patients was 16 days from ICU admission (95% CI, 9–19 days), 55 days from the first respiratory admission (95% CI, 18–284 days), and 1.05 years from primary diagnosis (95% CI, 0.34–1.75 years). Two patients discharged from hospital were alive at 31 December 2007: one was a 34-year-old man with an acute exacerbation of IPF (ICU length of stay, 15 days; APACHE III score, 31; and post-hospital follow-up, 11.0 years); and the other was a 77-year-old man admitted postoperatively after empyema

decortication (ICU length of stay, 1 day; APACHE III score, 37; and post-hospital follow-up, 1.82 years).

Kaplan–Meier survival curves for the three outcome measures are shown in Figure 1. For survival from ICU admission, in the Cox model, the APACHE III score (initially modelled linearly) was significant at $P=0.02$ (hazard ratio, 1.02; 95% CI, 1.004–1.031; ie, a 2% increase in hazard per unit increase in APACHE III score). The model was reasonably well specified (goodness-of-fit tests, $P \geq 0.18$; Harrell’s C statistic, 0.67) and demonstrated proportional hazards ($P=0.82$). Subsequent residual analysis indicated a non-linear effect of APACHE III, which was modelled using a cubic spline (Figure 2). Comparison of the linear and spline functions of APACHE III (at mean value of 82) in the Cox model are seen in the survivor curves of Figure 3, where the cubic spline had some advantage in terms of reduced width of the 95% point-wise confidence bands. No other covariates (age, sex, pre-hospital pulmonary function test results or therapy, time from diagnosis, time from first respiratory admission to index ICU admission, admission diagnosis and test results in the ICU, such as a positive sputum culture) were significant ($P \geq 0.17$).

For survival from the first respiratory admission, in the Cox model, only age at first respiratory admission (hazard ratio, 1.03; 95% CI, 1.00–1.07) was significant ($P=0.05$). The model was well specified (goodness-of-fit tests, $P \geq 0.18$; Harrell’s C statistic, 0.63) and showed proportional hazards ($P=0.49$). The demonstrated effect of age

Figure 2. Cox model effect of APACHE III score on survival from ICU admission modelled using a cubic spline



Cubic spline knots were set at 55 and 105 on the x-axis.

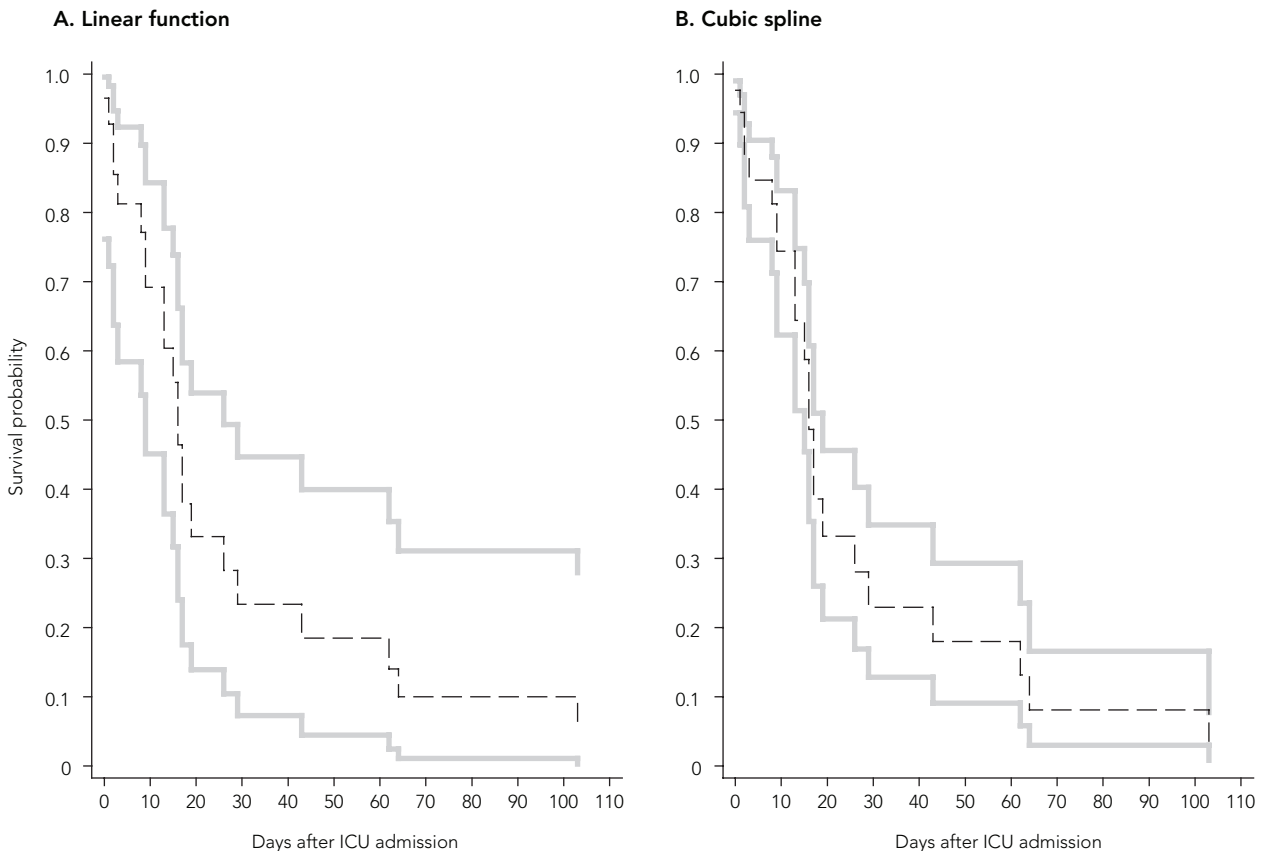
was linear. For the post-diagnosis Cox model, no covariates were significant (age at diagnosis, $P=0.13$; sex, $P=0.82$).

Within the analyses for survival from ICU admission and for survival from first respiratory admission, there was an apparent (univariate) favourable effect of having had pulmonary function tests performed (hazard ratios for binary variable scored 1 [=pulmonary function tests performed] or 0 [=no pulmonary function tests performed], 0.41; 95% CI, 0.17–0.99; $P=0.05$; and 0.44; 95% CI, 0.18–1.07; $P=0.07$, respectively). This may have indicated a selection bias dependent on physician supervision, although formal testing for heterogeneity using a random effects Cox model¹⁷ showed non-convergence because of small numbers.

Discussion

In this relatively small, but severely ill cohort, we found a dismal prognosis for patients with IPF admitted to the ICU, a finding consistent with that of other studies (Table 4).

Figure 3. Survival curves for survival beyond ICU admission, with 95% confidence bands, for linear and cubic spline APACHE III effect



Survivor function (dashed line), based on the cumulative hazard, with 95% point-wise confidence bands (solid grey lines) for survival beyond ICU admission, using Cox model estimates for APACHE III score as a linear (left panel) and cubic spline (right panel) function, at a (mean) APACHE III score of 82.

Table 4. Comparison of patient demographics and mortality between our study and others

Study	Patients	Diagnosis to ICU (months)*	Male/female	Age (years), mean (SD) [†]	Severity score (APIII) [†]	Ventilation (days) [†]	Length of stay (days) [†]		Mortality (%)		Long-term survival (days) [‡]	Pneumonia (%) [§]	IPF exacerbation (%) [§]
							ICU	Hospital	ICU	Hospital			
Stern (2001) ³⁰	23	31	19/4	53 (10)	na	3 (0.04–60) ^{¶¶}	na	na	4.5%	4.5%	na	22%	61%
Saydain (2002) ¹³	38	24**	25/13	68 (11)	60 (25)	10.5 (12.4)	4 (3–5) ^{¶¶}	12.5 (11–14) ^{¶¶}	45%	61%	60 ^{††}	31%	47%
Fumeaux (2001) ¹¹	14	68**	7/7	72 (8)	19 (6) ^{‡‡}	na	na	7.6 (4.8)	100%	100%	na	0	100%
Blivet (2001) ¹⁰	15	26.5	11/4	64 (10)	41 (8) ^{§§}	14.7 (12.5)	13.9 (11.2)	na	73%	93%	180 ^{¶¶}	40%	47%
Molina-Molina (2003) ¹²	20	14	13/7	67 (10)	na	na	na	na	100%	100%	na	40%	na
Al-Hameed (2004) ⁹	25	na	23/2	69 (11)	20 (2) ^{‡‡}	11 (2–17) ^{¶¶}	11 (8)	30 (1–67) ^{§§}	84%	96%	na	0	100%
Fernandez-Perez (2008) ²²	30***	6.3	na	na	57, 78 ^{†††}	na	na	na	na	na	24 ^{‡‡‡}	8.5%	76.5%
Current study	24	12.6	14/10	66 (16)	82 (37)	19.3 (23.2)	15.8 (21.2)	16 (0.1–103) ^{¶¶}	67%	92%	16 (9–19) ^{§§§}	42%	46%
						12 (0.37–103) ^{¶¶}	10 (0.1–103) ^{¶¶}						

APIII = APACHE III. na = not available. * Median time from IPF diagnosis to ICU admission. † Mean (SD) unless otherwise specified.

‡ Long term survival from ICU admission. § ICU admission diagnoses. ¶ Median (range). ** Mean.

†† 12 of 15 patients discharged from hospital died at a median of 2 months after discharge. ‡‡ APACHE II score.³⁵ §§ SAPS II score.³⁶

¶¶ One patient alive at 6 months after discharge, one lost to follow-up. *** Represents 32% of total cohort (n = 94).

††† Median APACHE III score for survivors and non-survivors of whole cohort. ‡‡‡ Median. §§§ Median (95% CI).

Admission to ICU

In our patients, the acute deterioration that led to ICU admission was attributed to pneumonia in 42%, exacerbation of IPF in 33%, cardiac failure in 13%, and expected (postoperative) respiratory failure in 13%. This profile is similar to only two^{10,13} of the seven recent comparator studies summarised in Table 4, and formal comparison with these studies is difficult because of the marked variation in time from IPF diagnosis to ICU admission, attendant severity of illness and the inclusion of other diagnostic categories of interstitial lung disease in three studies.^{11,12,22} The lower hospital mortality of 61% in the series of Saydain et al¹³ may have reflected less severe illness at ICU admission, at least compared with our study (mean APACHE III score, 60 [SD, 25] versus 82 [SD, 37] in our study; $P=0.01$).

The role of specific diagnostic and therapeutic modalities in the acute phase of IPF merits further attention.

Bronchoalveolar lavage: This was performed in few patients in our study, but others may use it more liberally in acute deterioration of IPF — for example, when there is a high index of suspicion for an infective aetiology, and microbiological analysis of sputum has not yielded any

result — although opportunistic infections have been reported as rare in IPF.⁴ When there is uncertainty about the diagnosis of interstitial lung disease,²³ bronchoalveolar lavage and invasive measures, such as open-lung biopsy, may be indicated.^{11,24}

Corticosteroids: Surprisingly, only one study⁹ specifically addressed the role of corticosteroids in this group of patients. The most common histological pattern specific to an acute exacerbation of IPF is that of diffuse alveolar damage, although organising pneumonia has also been described.²⁵ The former pattern is similar to that of late-phase acute respiratory distress syndrome (ARDS),²⁶ for which corticosteroids have recently been advocated,²⁷ and the latter may also be corticosteroid-responsive. Nevertheless, the therapeutic role of corticosteroids in acute exacerbation of IPF remains unclear,^{9,22,24,25} while the efficacy of corticosteroids in ARDS has recently been questioned.²⁸

Mechanical ventilation: It has been consistently reiterated that mechanical ventilation may be ineffective in improving oxygenation and subsequent survival.²⁹ However, the effect of specific mechanical ventilation modes on the outcome of IPF has not been systematically

addressed,^{10,11,30} although the derangements of lung mechanics have been well described.¹⁴ A recent study and commentary suggested that an “open lung strategy”, with high levels of PEEP, may be deleterious in IPF as opposed to ARDS,^{15,22} as patients with IPF may be expected to have a low percentage of recruitable lung and be subject to overdistension injury. Our study used modest maximal levels of PEEP — mean, 11 cmH₂O (SD, 3.5).

Prognostic indicators

The overall survival experience of the cohort was analysed as survival from diagnosis, from first (non-ICU) respiratory admission relating to IPF at the QEH, and from ICU admission (Figure 1). This analytical strategy appears to fully characterise this survival experience. The cohort size precluded a more fully developed multivariable predictive survival model, but the APACHE III score (for survival from ICU admission) and age (for survival from first respiratory admission) were intuitively reasonable survival predictors. The ability to delineate a non-linear mortality effect of the APACHE III score (Figure 2) is consonant with more recent trends in survival analysis,³¹ and has parallels with the modelled effect of this score in the APACHE III predictive algorithm;¹⁶ albeit the particular form of the non-linearity in the current study must be viewed judiciously because of the small numbers of patients. Of interest was the median 55-day survival from the first respiratory admission, suggesting, firstly, that the cohort had entered a stage with an irreversible downward course from this time, and, secondly, that any selection bias for survival dependent on physician supervision (see *Survival analysis*, above) was directed towards those patients with the most urgent symptoms.

Critique of methodology

Our study has potential shortcomings: data for this small, single-centre cohort were retrospectively collected; the long study time-span required patient identification using computerised electronic records, which may have been subject to patient misclassification; patient referral to the ICU may also have been subject to referring physician selection bias; and IPF diagnosis was not confirmed histologically in most patients, although this is consistent with current trends to rely more on non-invasive diagnostic measures. The seemingly long duration of ventilation and ICU length of stay may suggest disproportionate resource use associated with high in-hospital mortality. However, the cohort represents a very small fraction (0.004) of the total ICU admissions during the 11-year study period and, where appropriate summary statistics were available in comparator reports^{9,10,13} (Table 4), neither ventilation time nor ICU length of stay were statistically different from those found in our study ($P \geq 0.1$ for all comparisons).

The overwhelming in-hospital mortality contrasts with the short-term mortality previously reported for other patient cohorts with significant comorbidities in this ICU,^{32,33} and raises the question of appropriateness of admission. The small caseload of the current study and the noted improvement over time of overall mortality of ICU patients in the Australian and New Zealand context³⁴ militates against any rigid recommendation, and locates such decisions where they appropriately belong: timely discussion between referring and treating physicians, the patient and/or patient advocates.

Conclusions

Outcomes of patients with IPF admitted to the ICU are poor. The indications for mechanical ventilation appear uncertain.

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References

- 1 American Thoracic Society, European Respiratory Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International Consensus Statement. *Am J Respir Crit Care Med* 2000; 161: 646-64.
- 2 Gross TJ, Hunninghake, GW. Idiopathic pulmonary fibrosis. *N Engl J Med* 2001; 345: 517-25.
- 3 Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 176: 636-43.
- 4 Panos RJ, Mortenson RL, Niccoli SA, King TE. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. *Am J Med* 1990; 88: 396-404.
- 5 Hubbard R, Johnston I, Britton J. Survival in patients with cryptogenic fibrosing alveolitis: a population-based cohort study. *Chest* 1998; 113: 396-400.
- 6 Schwartz DA, Van Fossen DS, Davis CS, et al. Determinants of progression in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1994; 149: 444-9.
- 7 Raghu G, Depaso WJ, Cain K, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. *Am Rev Respir Dis* 1991; 144: 291-6.
- 8 Hyzy R, Huang S, Myers J, et al. Acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2007; 132: 1652-8.
- 9 Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J* 2004; 11: 117-22.

- 10 Blivet SM, Philit FM, Sab JM, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the ICU for respiratory failure. *Chest* 2001; 120: 209-12.
- 11 Fumeaux T, Rothmeier C, Jolliet P. Outcome of mechanical ventilation for acute respiratory failure in patients with pulmonary fibrosis. *Intensive Care Med* 2001; 27: 1868-74.
- 12 Molina-Molina M, Badia JR, Marin-Arguedas A, et al. Outcomes and clinical characteristics of patients with pulmonary fibrosis and respiratory failure admitted to an intensive care unit. A study of 20 cases. *Med Clin (Barc)* 2003; 121: 63-7.
- 13 Saydain G, Islam A, Afessa B, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med* 2002; 166: 839-42.
- 14 Nava S, Rubini F. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. *Thorax* 1999; 54: 390-5.
- 15 Baydur A. Mechanical ventilation in interstitial lung disease: which patients are likely to benefit? *Chest* 2008; 133: 1062-3.
- 16 Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest* 1991; 100: 1619-36.
- 17 Cleves MA, Gould WW, Gutierrez RG, Marchenko Y. An introduction to survival analysis using Stata. 2nd ed. College Station, Tex: Stata Press, 2008.
- 18 May S, Hosmer DW. Hosmer and Lemeshow type goodness-of-fit statistics for the Cox proportional hazards model. In: Balakrishnan N, Rao CR. *Advances in survival analysis: handbook of statistics*. Vol 23. Amsterdam: Elsevier, 2004: 383-94.
- 19 Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995; 48: 1503-10.
- 20 Royston P, Sauerbrei W. Multivariable modeling with cubic regression splines: a principled approach. *Stata J* 2007; 7: 45-70.
- 21 Royston P, Sauerbrei W. Some comparisons of MFP with splines. In: Royston P, Sauerbrei W. *Multivariable model-building: a pragmatic approach to regression analysis based on fractional polynomials for modelling continuous variables*. Chichester: John Wiley, 2008: 201-22.
- 22 Fernandez-Perez ER, Yilmaz M, Jenad H, et al. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. *Chest* 2008; 133: 1113-9.
- 23 Churg A, Muller NL. Cellular vs fibrosing interstitial pneumonias and prognosis: a practical classification of the idiopathic interstitial pneumonias and pathologically/radiologically similar conditions. *Chest* 2006; 130: 1566-70.
- 24 Ambrosini V, Cancellieri A, Chilosi M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. *Eur Respir J* 2003; 22: 821-6.
- 25 Churg A, Muller NL, Silva CI, Wright JL. Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. *Am J Surg Pathol* 2007; 31: 277-84.
- 26 Leaver SK, Evans TW. Acute respiratory distress syndrome. *BMJ* 2007; 335: 389-94.
- 27 Annane D. Glucocorticoids for ARDS: just do it! *Chest* 2007; 131: 945-6.
- 28 Peter JV, John P, Graham PL, et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 2008; 336: 1006-9.
- 29 Stern JB, Mal H, Peters SG. Mechanical ventilation in patients with pulmonary fibrosis. *Am J Respir Crit Care Med* 2003; 167: 1718-9.
- 30 Stern JB, Mal H, Groussard O, et al. Prognosis of patients with advanced idiopathic pulmonary fibrosis requiring mechanical ventilation for acute respiratory failure. *Chest* 2001; 120: 213-9.
- 31 Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006; 25: 127-41.
- 32 Moran JL, Green JV, Homan SD, et al. Acute exacerbations of chronic obstructive pulmonary disease and mechanical ventilation: a reevaluation. *Crit Care Med* 1998; 26: 71-8.
- 33 Moran JL, Solomon PJ, Williams PJ. Assessment of outcome over a 10-year period of patients admitted to a multidisciplinary adult intensive care unit with haematological and solid tumours. *Anaesth Intensive Care* 2005; 33: 26-35.
- 34 Moran JL, Bristow P, Solomon PJ, et al; Australian and New Zealand Intensive Care Society Database Management Committee (ADMC). Mortality and length-of-stay outcomes, 1993-2003, in the binational Australian and New Zealand intensive care adult patient database. *Crit Care Med* 2008; 36: 46-61.
- 35 Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818-29.
- 36 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. □