Title: Use of illness severity scores to predict mortality in interstitial lung disease patients hospitalised with acute respiratory deterioration

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ABSTRACT

Introduction

Hospitalisations relating to acute respiratory deteriorations (ARD) in Interstitial Lung Disease (ILD) have poor outcomes. Factors predicting adverse outcomes are not fully understood and data addressing the use of illness severity scores in prognostication are limited.

Objective

To validate the use of CURB-65 and NEWS-2 severity scores to predict mortality following ARD-ILD hospitalisation.

Methods

A dual-centre prospective observational cohort study of all adults (≥18y) hospitalised with ARD-ILD in Bristol, UK (n=179). Gender-Age-Physiology (GAP), CURB-65 and NEWS-2 scores were calculated for each eligible admission.

Receiver operating characteristics (ROC) curve analysis was used to quantify the strength of discrimination for NEWS-2 and CURB-65 scores. Univariable and multivariable logistic regression analyses were performed to explore the relationship between baseline severity scores and mortality.

Results

GAP showed some merit at predicting 30-day mortality (AUC=0.64, P=0.015); whereas CURB-65 showed modest predictive value for in-hospital (AUC=0.72, P<0.001) and 90-day mortality (AUC=0.67, P<0.001). NEWS-2 showed higher predictive value for in-hospital

(AUC=0.80, *P*<0.001) and 90-day mortality (AUC=0.75, *P*<0.001), with an optimal derived cut-off ≥6.5 found to be sensitive and specific for predicting in-hospital (83% and 63%) and 90-day (73% and 72%) mortality. In exploratory analyses, GAP score addition improved the predictive ability of NEWS-2 against 30-day mortality and CURB-65 across all time-periods.

Conclusion

NEWS-2 has good discriminatory value for predicting in-hospital mortality and moderate discriminatory value for predicting 90-day mortality. The optimal NEWS-2 cut-off value determined was the same as in a previous retrospective cohort, confirming the NEWS-2 score shows promise in predicting mortality following ARD-ILD hospitalisation.

KEY MESSAGES

What is the key question?

- Can NEWS-2 and CURB-65 be used to predict inpatient mortality in a cohort of patients with acute respiratory deterioration on a background of known interstitial lung disease?

What is the bottom line?

- The NEWS-2 score shows high sensitivity and specificity in predicting both 90-day and in-hospital mortality in patients hospitalised with ARD-ILD
- Whilst the CURB-65 score showed high sensitivity for predicting mortality, there was a low specificity, and did not add value to the predictive ability of the NEWS-2 score.

Why read on?

- This analysis included 179 patients from two study sites and provides, for the first time, prospective evidence for utilising NEWS-2 and CURB-65 as tools to predict in-hospital and post hospitalisation morbidity.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is considered the archetypal chronic progressive fibrotic Interstitial Lung Disease (ILD), which can have an unpredictable clinical course punctuated by sudden, severe acute respiratory deteriorations (ARD). ARD related hospitalisations in IPF patients are associated with poor patient outcomes, posing a significant burden on healthcare services.[1–4] ARD-IPF are categorised into parenchymal and extra-parenchymal causes within a conceptual framework.[1] Acute exacerbation (AE), defined within this framework describes rapid respiratory deterioration associated with new widespread parenchymal ground glass opacification (with or without consolidation) on the background of established fibrosis and is not fully explained by fluid overload or cardiac failure. Mortality associated with AE-IPF is high;[1,5] although, factors predicting adverse outcomes are not fully understood. Whilst originally described in IPF, both ARD and AE are increasingly considered to be features of other fibrosing ILDs; although, their epidemiology and triggers in non-IPF ILDs are less well understood, with no randomised controlled trials examining optimal management.[5]

The emergence of SARS-CoV-2 and resultant pandemic have severely impacted healthcare provision, with ILD patients at increased risk of severe COVID-19 disease, possibly attributable to immunosuppressive treatment in addition to their chronic lung changes.[6–8] Ensuring appropriate healthcare resource allocation and usage, especially with the significant ILD disease burden, may be aided by validated illness scores as predictors of mortality. The CURB-65 score was validated against 30-day mortality in pneumonia,[9] and subsequently validated against other conditions including sepsis. The National Early Warning Score-2 (NEWS-2) is used throughout UK hospitals to rapidly identify patients at risk of

deterioration,[10] and also to predict in-hospital mortality. There are few data on the use of illness severity scores to predict short to medium term outcomes following admission.[11–13]

Our previous single-centre, retrospective, observational cohort study of 172 IPF patients admitted with ARD, supported the use of CURB-65 and NEWS-2 illness severity scores to predict in-hospital and 90-day mortality.[4] ARD-IPF mortality was high irrespective of cause, in-line with mortality estimates from other published cohorts;[3] however, data also suggests AE-IPF mortality is higher compared to other parenchymal causes of ARD.[14]

The AvonCAP prospective observational study of acute lower respiratory tract disease (aLRTD) provided the opportunity to evaluate CURB-65 and NEWS-2 usage as predictors of mortality in a broad cohort of patients with ARD-ILD hospitalisations following the emergence of SARS-CoV-2. We describe the characteristics of a prospective cohort of patients hospitalised with ARD-ILD, comparing those patients with IPF and non-IPF ILDs and investigating factors associated with worse outcome.

METHODS

Study Design

A prospective, dual-centre observational cohort study undertaken at North Bristol and University Hospitals Bristol and Weston NHS Foundation Trusts, encompassing all secondary care institutions in Bristol, UK, as part of the AvonCAP study. The study was approved by the Health Research Authority East of England Ethics Committee, including use of Section 251 of the 2006 NHS Act approved by the Confidentiality Advisory Group (REC:20/EE/0157, ISRCTN:17354061).

Study Subjects

Patients hospitalised with worsening respiratory signs/symptoms between 1st August 2020 and 9th November 2021 were screened. Full inclusion and exclusion criteria are available on IRSCTN.[15] Only individuals with a multidisciplinary team (MDT)-confirmed diagnosis of ILD (either pre-existing or arising from the hospitalisation), including but not limited to IPF, were included in this analysis.

Collection of clinical data was undertaken on all eligible participants using a standardised REDCap proforma[16]. Lung Function Tests (LFTs) and 6-min walk test (6MWT) were included if conducted within 6-months of hospitalisation and were not performed specifically for this study. Gender-Age-Physiology (GAP), CURB-65 and NEWS-2 scores were calculated for each hospital admission.[9,17–19]

Case Definitions

The aetiology of ARD-ILD was categorised according to Collard's conceptual framework:

(1) Extra-parenchymal causes: pleural effusion, pneumothorax or pulmonary embolism,

(2) AE-ILD: diagnosed in accordance with broadened Collard *et al*. revised criteria [20] to include all fibrosing ILDs: previous/concurrent ILD, worsening dyspnoea <1 month duration, new bilateral ground-glass opacification (with/without consolidation) on CT imaging, superimposed on background of established fibrosis and not fully explained by cardiac failure/ fluid overload. AE-ILD was further sub-categorised into triggered (clear precipitant) or idiopathic.

(3) Not AE-ILD: other parenchymal ARD-ILD causes not attributed to an AE, including: non-pneumonic lower respiratory tract infection (NP-LRTI)/presumed NP-LRTI (defined in the context of a CT not clearly identifying a radiological cause for the deterioration or

unchanged CXR (presumed) but CRP>6mg/ml); pneumonia; cardiac failure/fluid overload; disease progression; and, those with non-specific trigger (no radiological cause demonstrated on CT imaging with CRP<6mg/ml; for example: anxiety, symptom control and/or palliation). (4) Not fully classified ARD-ILD: hospitalisation without CT imaging on admission but unaltered chest radiograph and CRP <6mg/ml and no clear trigger.

Outcome Measures

The primary outcome was to validate previously determined baseline CURB-65 score ≥3.5 and NEWS-2 score ≥6.5 as predictors of in-hospital mortality[4] in a broader group of patients with ILD.

Secondary outcomes were to determine the utility of the GAP score to predict in-hospital, 30- and 90-day mortality rates in patients with ARD-ILD, in addition to determining the overall in-hospital, 30- and 90-day mortality rates for patients with ARD-ILD, hospital length of stay (LOS), thereby highlighting any differences in mortality between IPF and non-IPF ARD cohorts.

Statistical Analysis

Categorical data were presented as numbers and proportions (n, %), continuous non-parametric data as medians and interquartile range (IQR). Either log rank test, Fisher's exact test or chi-square test was used where appropriate to analyse differences between groups.

For the primary analysis, univariable and multivariable logistic regression analyses were performed to explore the relationship between baseline severity scores and mortality. The factors used in the multivariable model were decided *a priori* and were smoking status, GAP

score, CURB-65 and NEWS-2 score. Receiver operating characteristic (ROC) curve analysis was used to quantify the strength of discrimination. Previous data suggested cut-offs of CURB-65>3.5 and NEWS-2>6.5, provided Area Under the Receiver Operating Curve (AUROC) estimates of 0.85 and 0.89 respectively, in the prediction of in-hospital mortality in hospitalised ARD-IPF.[4] Assuming an inpatient mortality rate approximating 20%.[4] a consecutive sample size of 175 patients would be sufficient to validate an AUROC≥0.8 with a lower 95% confidence interval (CI) of the AUROC exceeding a lower acceptability threshold of 0.7.[21] Power calculations were performed using the proprietary Power Analysis & Sample Size (PASS) software.

The impact of prognostic factors on survival was computed using a Kaplan-Meier analysis and multivariate Cox proportional hazards model. For all tests, a $P<0.05$ was considered statistically significant. Data were analysed using IBM SPSS v28.0.

RESULTS

Patient Demographics

Of the total 132,097 patients ≥18 years hospitalised in the study period: 179 patients had confirmed ARD with a multidisciplinary diagnosis of ILD (Figure 1A). The median age of patients was 75 years (IQR 72-84), 64% were male and 57% were ex-smokers (Table 1). IPF was the underlying diagnosis of 40% of the cohort, but a broad range of other ILD diagnoses existed, including: unclassifiable ILD (13%), hypersensitivity pneumonitis (HP) (12%), and connective tissue disease associated-ILD (10%) (Table 1). *De novo* presentations with ILD were infrequent (3% ILD admissions). Patients had moderately restrictive disease (median FVC% predicted 75 (IQR 63-91), TLCO 44% (IQR 33-58) and a median GAP score of 4

(IQR 3-5), corresponding to GAP stage II. Approximately one third of patients had at least 2 or more (31%, n=56) concurrent medical co-morbidities. Overall, vaccination rates were high in the cohort: 75% of patients having received pneumococcal and seasonal influenza vaccination by the time of admission, and 83% of eligible patients (Supplementary Data 1) having received at least one dose of a COVID-19 vaccination prior to admission.

IPF patients were statistically older than those with non-IPF ILD diagnoses (IPF 81 years vs non-IPF 77 years, P=0.0068), more likely to be male (IPF 77% vs non-IPF 55%, Fisher's exact test, P =0.004), with lower TLCO % predicted (IPF 38% vs non-IPF 54%, P=0.0002) and higher GAP scores (IPF 5 vs non-IPF 4, P<0.0001) on hospitalisation. IPF and non-IPF ILD patients had comparable baseline spirometry values (Table 1).

Underlying Aetiology

Most (79%) ARD-ILD admissions were due to parenchymal causes other than AE-ILD (Figure 1B). Pneumonia was the most common parenchymal cause (57%, 77/141); the vast majority were community-acquired (83% of pneumonias, n=63), with COVID-19 pneumonitis in eleven patients (14%). Other parenchymal causes included cardiac failure (n=21, 15%), NP-LRTI (n=24, 17%, including 3 patients with symptomatic COVID) and disease progression in n=5 (4%). An extra-parenchymal pathology was considered the cause of ARD in 12 patients (7%); 7 with pulmonary embolism, 3 with pleural effusion/empyema, with pneumomediastinum and anaphylaxis in the remaining patients.

Non-specific triggers of ARD were identified in approximately 10% of patients and these admissions were related to requirements for palliation and symptom control, including anxiety and breathlessness. AE-ILD was rare in this cohort (n=3, 2%) and seen in patients

with fibrotic hypersensitivity pneumonitis and IPF. Due to low incidence of AE-ILD we were not able to perform analyses to determine differences between patients admitted with AE-ILD and other parenchymal causes.

232 **Table 1: Characteristics of adults hospitalised with ARD-ILD**

Characteristic	ARD-ILD n = 179	IPF n = 70	Non IPF n = 109	*P*-value
Male, n (%)	114 (64)	54 (77)	60 (55)	**0.0040**
Age (years), median (IQR)	79 (72-84)	81 (75-86)	77 (70-83)	**0.0068**
Smoking Status, n (%)				0.2537
Current	9 (5)	4 (6)	5 (5)	
Ex-smoker	102 (57)	48 (69)	54 (50)	
Never	53 (30)	14 (20)	39 (36)	
Unknown	15 (8)	4 (6)	11 (10)	
Ethnicity, n (%)				0.7566
Caucasian	148 (83)	58 (83)	90 (83)	
Other	11 (6)	6 (9)	5 (5)	
Unknown	20 (11)	6 (9)	14 (13)	
CCI, median (IQR)	5 (4-6)	5 (4-6)	5 (3-6)	0.8765
Aetiology ILD, n (%)				N/A
IPF	70 (39)	70 (39)	-	
Unclassifiable	23 (13)	-	23 (13)	
Hypersensitivity pneumonitis	22 (12)	-	22 (12)	
CTD-ILD	17 (10)	-	17 (10)	
Smoking related ILD	14 (8)	-	14 (8)	
CPFE	9 (5)	-	9 (5)	
NSIP	8 (5)	-	8 (5)	
Sarcoid	6 (3)	-	6 (3)	
Asbestosis	4 (2)	-	4 (2)	
Other □	6 (3)	-	6 (3)	
Baseline PFTs, median (IQR)				
Lung function				
FEV1 % predicted	78 (66-93), n=168	81 (69-93), n=68	75 (63-93), n=100	0.5627
FVC % predicted	75 (63-91), n=168	75 (64-89), n=68	77 (63-96, n=100	0.5324
TLCO % predicted	44 (33-58), n=137	40 (30-46), n=58	54 (37-61), n=79	**0.0002**
6MWT distance (m)	240 (155-311), n=133	240 (130-290), n=60	245 (168-354), n=73	0.7552
6MWT minimum sats (%)	87 (84-90) n=133	87 (84-89), n=60	87 (84-90), n=73	0.8129
Total GAP score	4 (3-5), n=150	5 (4-6), n=61	4 (3-5), n=89	**<0.0001**
Admission Severity Scores				
CURB-65, median (IQR)	2 (1-4)	2 (1-4)	1 (1-3)	**0.0096**
NEWS-2, median (IQR)	6 (3-8)	6 (3-8)	5 (2-8)	0.4246
Respiratory Support, n (%)				
None	20 (11)	10 (14)	10 (9)	0.1382
Oxygen	159 (89)	60 (86)	99 (91)	0.1482
HFNO	20 (11)	8 (11)	12 (11)	1.0000
NIV	8 (4)	5 (7)	3 (3)	0.2123
IMV	1 (1)	0 (0)	1 (1)	0.4033
Treatment, n (%)				
Received antibiotics (>2 days)	139 (78)	53 (74)	86 (79)	0.4391
Received corticosteroids	49 (27)	18 (26)	31 (28)	0.7702
Length of stay, median (IQR)				
Hospitalisation days	6 (3-11)	7 (3-11)	6 (3-11)	0.5451
Mortality, n (%)				
In-hospital mortality	34 (19)	17 (24)	17 (16)	0.1848
30-day mortality	42 (23)	21 (30)	21 (19)	0.0901
90-day mortality	69 (39)	33 (47)	36 (33)	0.0614
Survival days, median (IQR)	59 (10-144), n=101	23 (10-23), n=41	79 (13-144), n=60	**0.0417**

P-values represent the result of a Log-rank Test or Fisher's exact test between IPF and non-IPF groups

 Other includes lymphocytic interstitial pneumonia, Langerhan's cell histiocytosis, pleuro-parenchymal fibroelastosis, Rosai-Dorfman, organising pneumonia.

6MWT, 6-minute walk test; ARD, acute respiratory deterioration; CCI, Charlson comorbidity index; CPFE, combined pulmonary fibrosis & emphysema; CTD-ILD, connective tissue disease ILD; GAP, gender, age and physiology score; HFNO, high flow nasal oxygen; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IMV, invasive mechanical ventilation; IQR, interquartile range; NIV, non-invasive ventilation NSIP, non-specific interstitial pneumonia; PFTs, pulmonary function tests

Primary Outcome

Over half of all patients hospitalised with an ARD-ILD had a CURB-65≥2 (n=99, 55%) and NEWS-2 ≥5 (n=114, 64%) on admission. Patients with ARD-IPF had a statistically higher baseline CURB-65 compared to those with non-IPF ARD-ILD diagnoses (median CURB-65 2 [IQR 1-4] versus 1 [IQR 1-3], *P*=0.0096), but baseline NEWS-2 scores were comparable (median NEWS-2 6 [IQR 3-8] versus 5 [IQR 2-8] respectively, *P* >0.05) (Table 1).

GAP score was found to have diminishing utility for in-hospital (AUC=0.604, *P*=0.087) and some merit at 30-days (AUC=0.642, *P*=0.015). CURB-65 showed modest predictive value for in-hospital (AUC=0.715, *P*<0.0001) and 90-day mortality (AUC=0.672, *P*<0.0001), with the optimal derived cut-off CURB-65≥2.5 in our previous study[4] had high specificity (75, 88% respectively) but low sensitivity (57, 46% respectively) (Table 2). The optimal derived cut-off for CURB-65 in this cohort was 3.5. The NEWS-2 showed higher predictive value for in-hospital (AUC=0.803, *P*<0.0001) and 90-day mortality (AUC=0.751, *P*<0.0001). The optimal cut-off for NEWS-2≥6.5 was found to have high sensitivity (73%) and specificity (72%) for predicting 90-day mortality, in contrast to high sensitivity (83%) and moderate specificity (63%) for predicting in-hospital mortality (Table 2).

As the CURB-65 score correlated moderately to NEWS-2 score (R=0.552, *P*<0.0001), the combined ability of these two scores to predict mortality was assessed (Table 2). NEWS-2 retained significance to predict 90-day and in-hospital mortality after allowing for the effect of CURB-65 score (OR 1.34, *P*<0.0001, and OR 1.47, *P*<0.0001, respectively); however, CURB-65 was no longer a significant predictor after controlling for NEWS-2 for 90-day (OR 1.34, *P*=0.1648) or in-hospital mortality (OR 1.423, *P*=0.1791) (Supplementary Data 3). The addition of the GAP score improved the ability of the CURB-65 score to predict mortality (Table 2), with both GAP and CURB-65 retaining significance in each other's presence. In contrast, the GAP score only improved the ability of the NEWS-2 score to predict 30-day mortality.

Secondary Outcomes

The median length of stay for patients admitted with an ARD-ILD was 6 days, but variability was observed across the cohort (IQR 3-11 days). Small numbers of patients received advanced respiratory support during their admission (n=29, 16%) although supplementary oxygen was frequently prescribed (n=159, 89%) (Table 1). ARD-ILD associated mortality was high; 20% of hospitalisations resulted in death, with 30- and 90-day mortality following admission of 24% and 38% (n=68) respectively (Table 1). Survival curve analysis indicated that patients admitted with ARD-IPF had higher in-hospital and 90-day mortality than patients with non-IPF-ARD (Figure 2). Univariate Cox regression analysis indicated that increasing NEWS-2 score was associated with higher mortality risk in-hospital and at 90-days; however, increased admission CURB-65 scores were not associated with an increased mortality risk (Table 3). Neither were higher admission CURB-65 nor NEWS-2 scores found to be associated with increased hazard of in-hospital mortality.

Table 2: Outcomes of ROC curve analysis for evaluating optimal cut-off values for CURB-65, NEWS-2 and GAP scores, correlating with ARD-ILD mortality

Evaluation of the receiver operator curve (ROC) curve analysis for CURB-65, NEWS-2 and GAP scores correlate with 30- and 90-day mortality, in addition to in-hospital mortality.

	AUC	95% CI	*P*-value	Decision Point	Sensitivity	Specificity	Youden's Index (J)
SINGLE DISEASE SEVERITY SCORES							
CURB-65							
In-hospital mortality	0.715	0.620-0.810	<0.0001	3.5	0.200	0.965	0.17
				2.5	0.571	0.746	0.32
30-day mortality	0.650	0.553-0.746	0.0021	1.5	0.476	0.737	0.21
90-day mortality	0.672	0.591-0.753	<0.0001	3.5	0.130	0.973	0.10
				2.5	0.464	0.882	0.25
NEWS-2							
In-hospital mortality	0.803	0.731-0.875	<0.0001	6.5	0.829	0.634	0.46
30-day mortality	0.750	0.669-0.831	<0.0001	6.5	0.762	0.642	0.40
90-day mortality	0.751	0.680-0.822	<0.0001	6.5	0.725	0.718	0.44
GAP							
In-hospital mortality	0.604	0.491-0.717	0.0869	4.5	0.607	0.554	0.16
30-day mortality	0.642	0.541-0.744	0.0151	3.5	0.871	0.353	0.22
90-day mortality	0.564	0.471-0.658	0.1887	4.5	0.545	0.568	0.11
COMBINATION DISEASE SEVERITY SCORES							
CURB-65 and NEWS-2							
In-hospital mortality	0.805	0.731-0.879	<0.0001	0.157	0.857	0.620	0.48
30-day mortality	0.681	0.589-0.822	<0.0001	0.225	0.624	0.681	0.40
90-day mortality	0.757	0.687-0.827	<0.0001	0.392	0.710	0.682	0.39
CURB-65 and GAP							
In-hospital mortality	0.764	0.671-0.856	<0.0001	0.207	0.679	0.739	0.41
30-day mortality	0.761	0.677-0.846	<0.0001	0.140	0.903	0.504	0.41
90-day mortality	0.727	0.646-0.809	<0.0001	0.335	0.673	0.663	0.34
NEWS-2 and GAP							
In-hospital mortality	0.802	0.745-0.895	<0.0001	0.239	0.679	0.802	0.48
30-day mortality	0.810	0.732-0.888	<0.0001	0.177	0.839	0.639	0.48
90-day mortality	0.752	0.675-0.828	<0.0001	0.342	0.782	0.642	0.43

AUC, area under curve; CI, confidence interval; GAP, Gender, Age, Physiology Score; ROC, receiver operator characteristics. ROCs are provided within Supplementary Data 2 and 3.

Table 3: Association of baseline patient factors with in-hospital mortality and 90-day mortality following hospitalisation with ARD-ILD

Cox proportional hazard regression univariate analysis

Analysis	Factor	Wald	HR	*P*-value	95% CI
In hospital mortality	GAP score	0.365	1.089	0.5452	0.826-1.435
	Smoking Status	3.102	2.022	0.0778	0.924-4.428
	CURB-65 score	3.163	1.565	0.0747	0.955-2.562
	NEWS-2 score	3.841	1.188	0.0501	1.000-1.411
90-day mortality	GAP score	1.020	0.773	0.3132	0.469-1.274
	Smoking Status	2.016	1.676	0.1558	0.822-3.419
	CURB-65 score	1.089	0.753	0.2967	0.442-1.283
	NEWS-2 score	4.251	1.231	**0.0391**	1.010-1.501

CI, confidence interval; GAP, Gender, Age, Physiology Score; HR, hazard ratio.

DISCUSSION

The identification of patients with poor prognosis among those with ARD-ILD remains a significant challenge and there are limited data addressing the utility of illness severity scores to predict outcomes of these patients. This prospective study suggests that, as a predictor of mortality in this patient cohort, the NEWS-2 score has good discriminatory value for predicting in-hospital mortality and moderate discriminatory value for predicting 90-day mortality in patients with ARD-ILD. To our knowledge, this is the first prospective evidence for utilising NEWS-2 as a tool to predict in-hospital and post hospitalisation morbidity. A previous retrospective cohort study conducted at one of the study hospitals found that both NEWS-2 and CURB-65 risk stratification tools were independent predictors of mortality in patients with IPF.[4] The current study therefore confirms the findings of this previous retrospective cohort[4] and hence NEWS-2 may represent a simple tool to help prognostication. Notably, the optimal derived cut-off value for NEWS-2 in predicting mortality across inpatient, 30- and 90-days was NEWS-2 ≥6.5, the same in both this prospective patient cohort and our previously reported retrospective cohort.[4]

The CURB-65 score was found to have little additional benefit for predicting mortality, either as an individual predictor or when used in exploratory analyses with NEWS-2. Furthermore, we found that CURB-65 was able to predict both 90-day and in-hospital mortality in ARD-ILD with high specificity but low sensitivity, in keeping with previous data from our IPF cohort[4]. Aligning with these findings, Yamazaki *et al* found that CURB-65, Pneumonia Severity Index (PSI) and Sequential Organ Failure Assessment (qSOFA) were all predictive of inpatient mortality from pneumonia in a retrospective study of 79 patients with IPF.[22] In that study, the optimal CURB-65 cut-off value was ≥3.0, differing slightly from the value derived in our previous retrospective IPF cohort,[4] but contrasting with the optimal cut-off

≥2.5 derived in this current prospective ILD cohort. Notably, the CURB-65 score did not add value to the ability of the NEWS-2 score to predict poor outcomes. In contrast, exploratory analyses indicate there is some evidence of increased predictive ability on outcomes when NEWS-2 and GAP scores are used in tandem. Overall, these findings from different centres and patient populations suggest that the disease severity scores show promise in predicting poor outcome following hospitalisation with acute respiratory deterioration.

As reported before the emergence of SARS-CoV-2, patients hospitalised with ARD-IPF had a poor prognosis.[4,23–25] The median survival in this cohort was 23 days, slightly shorter than the survival times in the literature ranging between 1 and 4 months after AE-IPF.[26–29] Whilst in-hospital and 90-day mortality rates were significantly higher in the IPF group than the non-IPF group, all admissions related to an ARD were associated with significant mortality; 24% and 38% for 30- and 90-day mortality, respectively. Our in-hospital mortality data supports early and frank discussions between patients/families and clinicians surrounding the high mortality associated with ARD, even in the context of potentially 'treatable' causes e.g. infection and pulmonary embolism. Furthermore, the high short-term mortality after discharge may prompt clinicians to consider early discussions surrounding palliation and/or transplantation in suitable candidates.

There were few admissions secondary to AE-ILD, which prevented further detailed analyses of any differences in the mortality between AE-ILD and other parenchymal causes of ARD. Teramachi *et al* showed 90-day mortality of AE-IPF patients was significantly higher than ARD due to other parenchymal causes (46% (16/35) vs 17% (12/71) respectively; P=0.002).[14] It is not possible to ascertain fully to what extent healthcare access and patient behaviour during the pandemic affected these outcomes. The Task Force for Lung Health

suggested that over a third of people with pre-existing lung problems felt pressure to avoid or delay seeking treatment.[30] Hence, patients may have delayed presentation to hospital. Alternatively, the emergence of a novel pathogen may have affected outcomes of patients with ARD, either directly or indirectly through changes in the epidemiology of other acute respiratory infection, treatment pathways or other aspects of patient healthcare provision. In non-ILD patients hospitalised with SARS-CoV-2 infection, NEWS-2 correlates moderately well with severe outcomes such as ITU admission, positive airway pressure support or death; however, there were no such significant correlations for CURB-65 (P>0.05).[31]

This study has many strengths. It was undertaken as a prospective two site cohort study which screened hospital admissions for signs/symptoms of acute respiratory disease. This study therefore does not rely on ICD-10 coding or solely on data-linkage. There were minimal missing data, and the study includes adults who lack capacity to consent through a consultee and by specific authorisation to use certain data without consent, thereby ensuring full ascertainment of ARD-ILD during this period. The medical records were linked with community records to obtain detailed and accurate data for each study participant.

There are also some limitations of this study. First, we assessed ARD-ILD at both acute care NHS hospitals in Bristol and 83% of this cohort is Caucasian; therefore, we cannot be sure that results are generalisable to other patient populations. Second, we used vital statistics to determine mortality, and did not ascertain the specific cause of death. Third, the number of acute exacerbations in this cohort was low, we were therefore unable to confirm our previous findings that mortality associated with ARD-ILD was high, irrespective of the underlying cause for the deterioration. Lastly, it is difficult to determine whether healthcare access may have affected time to hospitalisation and hence outcomes, as previously mentioned.

CONCLUSION

Simple illness severity scores may permit refinement of ARD management of ILD patients and if survival to discharge is achieved, permit early discussion with patients, referral to transplantation or palliative care planning as appropriate.

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FIGURE LEGENDS

Figure 1. Adults hospitalised with acute respiratory deterioration of interstitial lung disease

(A) Flow diagram of study participants and (B) aetiology of acute respiratory deterioration of Interstitial lung disease (ARD-ILD).

ARD; acute respiratory deterioration; AE-ILD, acute exacerbation of interstitial lung disease; LRTI, lower respiratory tract infection; COVID-19, coronavirus disease 2019; HF, heart failure.

+n=11 COVID-19 pneumonia, one aspiration pneumonia, one hospitalised pneumonia, remainder deemed to be community acquired pneumonia

*including 3 with symptomatic COVID-19 but no CXR infiltrates

^ unclassified – CT not performed and CRP <50.

Figure 2: ARD-ILD survival curve analysis

Kaplan Meier survival curves for (A) in-hospital and (B) 90-day mortality, for patients admitted with ARD-IPF (green line) and non-IPF ARD-ILD (blue line).

AUTHOR CONTRIBUTIONS

CH, RW, PW, AF and SLB generated the research question and analysis plan. The data for this study was collected by the AvonCAP Research Team, CH, RW, JR, MGG and ZSB. CH, MGG, ZSB and RW verified the data. RW, CH, PW, AF and SLB undertook data analysis. All authors were involved in the final manuscript preparation and its revisions before publication. AF and SB provided oversight of the research.

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DATA SHARING

The data used in this study are sensitive and cannot be made publicly available without breaching patient confidentiality regulations. Therefore, individual participant data and a data dictionary are not available to other researchers.

DECLARATION OF INTEREST

CH is Principal Investigator of the AvonCAP study, which is an investigator-led University of Bristol study funded by Pfizer, Inc, and is currently a member of the BTS Pulmonary Infection Specialty Advisory Group (SAG). AF is a member of the Joint Committee on Vaccination and Immunization (JCVI) and chair of the World Health Organization European

525 Technical Advisory Group of Experts (WHO ETAGE) committee. In addition to receiving
526 funding from Pfizer as Chief Investigator for this study, he leads another project investigating
527 transmission of respiratory bacteria in families jointly funded by Pfizer and the Gates The
528 other authors declare no competing interests.

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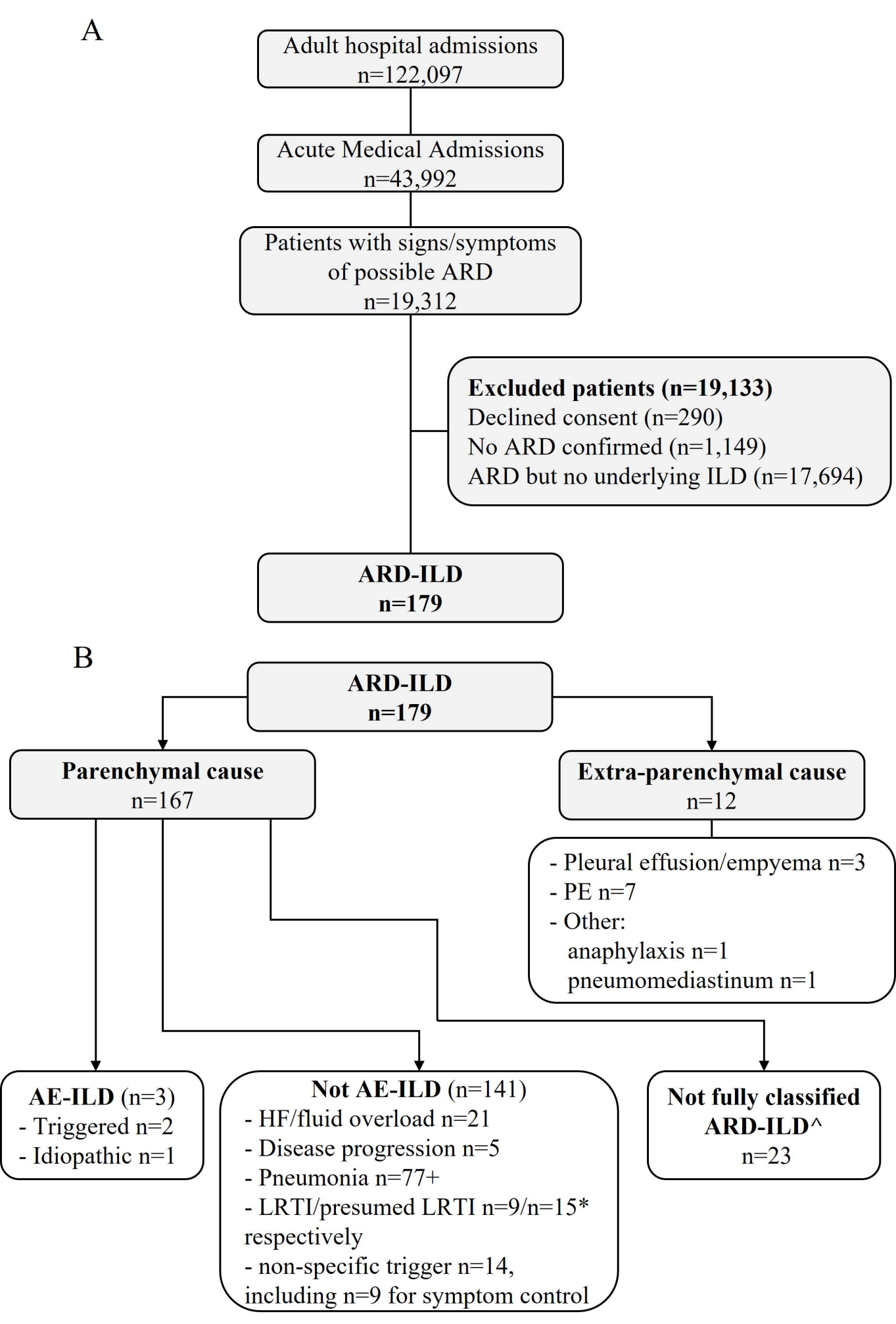
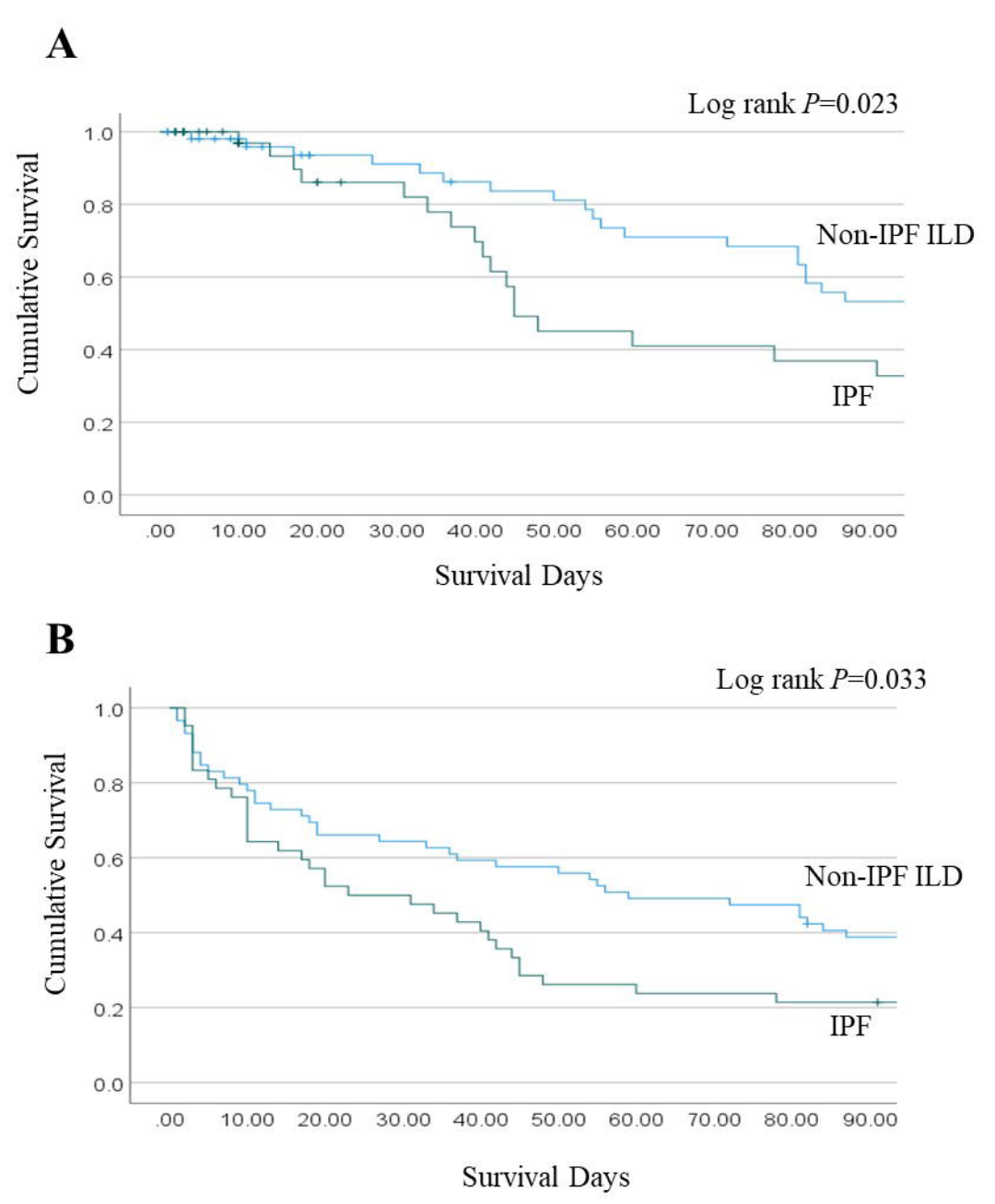

A
Adult hospital admissions
n=122,097
Acute Medical Admissions
n=43,992
Patients with signs/symptoms
of possible ARD
n=19,312
Excluded patients (n=19,133)
Declined consent (n=290)
No ARD confirmed (n=1,149)
ARD but no underlying ILD (n=17,694)
ARD-ILD
n=179
B
ARD-ILD
n=179
Parenchymal cause
n=167
Extra-parenchymal cause
n=12
- Pleural effusion/empyema n=3
- PE n=7
- Other:
anaphylaxis n=1
pneumomediastinum n=1
AE-ILD (n=3)
- Triggered n=2
- Idiopathic n=1
Not AE-ILD (n=141)
- HF/fluid overload n=21
- Disease progression n=5
- Pneumonia n=77+
- LRTI/presumed LRTI n=9/n=15*
respectively
- non-specific trigger n=14,
including n=9 for symptom control
Not fully classified
ARD-ILD^
n=23


A
Log rank P=0.023
Non-IPF ILD
IPF
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
90.00
Survival Days
B
Log rank P=0.033
Non-IPF ILD
IPF
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
90.00
Survival Days