

ORIGINAL ARTICLE

Oxygen exchange and C-reactive protein predict safe discharge in patients with H1N1 influenza

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Summary

Background: Pandemic influenza has potential to overwhelm healthcare resources. There is uncertainty over performance of existing triage tools for hospital admission and discharge decisions.

Aim: Our aim was to identify clinical criteria that predict safe discharge from hospital and develop a pragmatic triage tool to guide physician decision-making.

Design: We retrospectively examined an existing database of patients who presented to the Royal Liverpool University Hospital during the 2010–11 influenza pandemic.

Methods: Inclusion criteria: patients ≥ 18 years, with PCR confirmed H1N1 influenza. Exclusion criteria: died in the emergency department or case notes unavailable. Successful discharge was defined as discharge within 24 h of presentation and no readmission within 7 days.

Results: Eighty-six patients were included and 16 were successfully discharged. Estimated P/F ratio and C-reactive protein predicted safe discharge in a multivariable logistic regression model (AUC 0.883). A composite univariate predictor (estimated P/F minus C-reactive protein, AUC 0.877) was created to calculate specific cut off points for sensitivity and specificity. A pragmatic decision tool was created to incorporate these thresholds and relevant guidelines. Discharge: SpO₂ (in air) $\geq 94\%$ and CRP < 50 . Observe: SpO₂ $\geq 94\%$ and CRP > 50 or SpO₂ $\leq 93\%$ and CRP < 50 . Admit: SpO₂ $\leq 93\%$ and CRP > 50 .

Conclusions: We identified that oxygen exchange and CRP, a marker of acute inflammation, were the most important predictors of safe discharge. Our proposed simple triage model requires validation but has the potential to aid clinical decisions in the event of a future pandemic, and potentially for seasonal influenza.

Purpose of study

Pandemic influenza is regarded as a threat to UK national security.¹ In response, the UK Department of Health has drawn up detailed plans such as the 'Health and Social Care Influenza

Pandemic Preparedness and Response' to guide clinicians in the event of a future outbreak². It is anticipated that any future pandemic would impose significant impact in both primary and secondary care and potentially overwhelm demand for critical

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care resources. Successful implementation of emergency triage measures to manage surges in demand depends upon public and clinician confidence in accuracy and fairness of the tool.³

In the UK, a clinical assessment package was proposed for pandemic H1N1 to guide hospital admission versus early discharge decisions when hospital capacity is limited.⁴ Multiple investigations have examined clinical factors that predict the need for critical care^{5–8} and factors that differentiate influenza from non-influenza induced illness^{9–13} in patients admitted to hospital during the 2010–11 H1N1 influenza pandemic. However, the parameters for hospital discharge described by the clinical assessment tool have not subsequently been validated in patients with confirmed H1N1 influenza. Given the increasing pressures on bed capacity, there is a pressing need for decision-making support around admission for influenza.¹⁴

Previously, we examined a retrospective cohort of patients with confirmed H1N1 influenza for factors that predict the need for mechanical ventilation.⁵ This work demonstrated that P/F ratio, a simple measure of oxygen exchange was a superior predictor of mechanical ventilation compared to other proposed (more complex) triage tools. However, factors that predict safe discharge after acute presentation have not been examined. Safe discharge decisions are important in an epidemic setting; patients should not be sent home to subsequently deteriorate but conversely, admissions are constrained by finite resource. Our aim was to examine clinical factors used to assess patients who acutely presented to hospital with influenza and retrospectively determine association with the decision to discharge. Subsequently, our aim was to develop a pragmatic triage tool that can be used by treating clinicians in the event of a future influenza pandemic.

Study design

Patients

We retrospectively examined an existing database of patients with confirmed H1N1 influenza who presented to the Royal Liverpool University Hospital, UK, an inner-city tertiary care centre with >28 000 accident and emergency (A&E) department admissions per year (November 2010–January 2011).⁵ This database was supplemented with radiographic findings, readmission rates and 'quick' sequential organ failure assessment (qSOFA) scores.¹⁵ Inclusion criteria were the following: patients ≥ 18 years, with H1N1 influenza infection confirmed by reverse transcriptase polymerase chain reaction (PCR) who presented with acute illness to the Royal Liverpool University Hospital. Patients eligible for the study were either admitted to hospital or discharged home within 24 h of presentation. Patients were excluded if they tested negative for H1N1 influenza, died in the emergency department or if case notes were unavailable. Early discharge was defined as discharge within 24 h of presentation. Successful discharge was defined as no re-admission within 7 days of initial presentation. The UK NHS Research Ethics Service granted approval for this project (13/LO/0609) and individual patient consent was not required.

Clinical variables and triage scores

Data regarding patient demographics, comorbidities, physiological observations, clinical laboratory tests, arterial blood gases and oxygen saturations collected within the first 24 h of admission were analysed. P/F ratio is calculated by dividing the partial pressure of arterial oxygen (PaO₂) in mmHg, by the

fraction of inspired oxygen (FiO₂). Where an arterial blood gas was unavailable, we employed a validated P/F ratio estimation calculation using SpO₂ and FiO₂.¹⁶ SOFA, Simplified Triage Severity Score (STSS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated during initial assessment and after 24, 48 and 120 h. The qSOFA score for each patient was also calculated.¹⁵

Chest radiograph scoring

Chest radiographs were stored in the Picture Archiving and Communications System (PACS) and viewed in the Digital Imaging and Communications in Medicine (DICOM) format. Only the first image after initial assessment was scored. An experienced consultant radiologist scored the radiographs (gold standard) using a previously published objective 5-point scoring system (see [Supplementary material, Figure 1](#).¹⁷ A trainee in acute care, an Intensive Care trainee and a medical student also independently reviewed and scored each chest radiograph. We examined junior doctor interpretation to determine agreement with gold standard consultant radiologist reporting. Each reviewer was blinded to the clinical history, patient outcome and radiologist report, but was permitted to comment on additional findings. Each member was given the opportunity to review scores that were ± 2 points different from any of the other scores.

Statistical analysis

The primary outcome of the study was the ability of routine clinical investigations to predict successful early discharge (definitions above). This included the previously described Simplified triage severity score (STSS),¹⁸ in addition to a 5-point chest X-ray quantification score¹⁷ and the 'quick' sequential organ failure assessment (qSOFA) score.¹⁵ All data were analysed using STATA 13.1 (Statacorp. 2013, US). The outcome variable was binary – early successful discharge or admission to hospital. Clinical variables were checked for normal distribution with Q–Q plots and the Shapiro–Wilk test. For normally distributed data, differences between the two patient groups were assessed with the independent t-test and data presented as means with standard deviation. For non-normally distributed data, differences between groups were assessed with the Mann–Whitney U Test and data depicted as medians with interquartile ranges. To assess the predictive capacity of the chest radiograph scoring system, dummy variables were created for the gold standard chest radiograph scores, which were then placed into a logistic regression model. Differences in scores were calculated between reviewers and a weighted Cohen's kappa statistic (κ) employed for inter-rater reliability. Agreement was defined by weighted kappa scores of 0.8–1.0 as 'very good', 0.6–0.8 as 'good', 0.4–0.6 as 'moderate', 0.2–0.4 as 'fair' and below 0.2 as poor.¹⁷ Univariate and subsequently, multivariable logistic regression were utilised to fit a predictive algorithm. The multivariate model was constructed by backward elimination of non-significant variables ($P > 0.1$). Subsequently, a univariate variable (estimated P/F ratio minus CRP, no weighting) was created, a receiver operating characteristic (ROC) curve calculated and cut-off values determined for sensitivity and specificity. Area under the curve (AUC) values of 0.7, 0.8 and 0.9 were defined as 'fair', 'good' and 'excellent' predictors, respectively.¹⁹

Results

Eighty-six patients were included in the study. Sixteen patients were discharged within 24 h of presentation and none required readmission within 7 days. Sixty-one patients presented to the accident and emergency department, 24 were directly admitted to acute medical assessment areas and one patient was an inter-hospital critical care transfer for tertiary ventilatory management. Median length of stay for discharged patients was 14 h (IQR 2.5–21.5) and 133 h (IQR 71–292) for those admitted. Ten patients died in this cohort (all admitted to hospital). Arterial blood gas samples were taken in 59 patients and permitted direct calculation of P/F ratio; estimated P/F ratios were calculated in all patients as a logarithmic transformation of SpO₂ and FiO₂.¹⁶ Patients who were discharged early were younger (median 31 vs. 45 $P=0.028$), had a lower CRP (median 27 vs. 112 $P=0.001$) and higher albumin (mean 41.5 vs. 36.1, $P=0.008$) compared with those who were admitted. Estimated and measured P/F ratios were higher in those discharged early (357.3 vs. 336.7, $P=0.059$ and 435.5 vs. 233.0, $P<0.001$, respectively). Differences between other measured variables were non-significant and are displayed in [Supplementary material Table S1](#).

There were significant differences in SOFA, qSOFA and STSS and CXR scores between patients discharged and admitted – [Table 1](#). For the chest X-ray score, we found good agreement between the consultant radiologist and those of the acute care trainee ($\kappa=0.661$) and the medical student ($\kappa=0.661$). There was moderate agreement between the consultant radiologist and intensive care trainee ($\kappa=0.588$). CURB-65 score was not associated with safe discharge in this cohort ($P=0.096$).

Univariate logistic regression analyses were performed to determine association between significant parameters and safe discharge ([Table 2](#)). Subsequently, a multivariate logistic regression model was constructed ([Table 3](#)) and a receiver operator curve generated (AUC 0.883). Using this information, we constructed a new univariate variable: estimated P/F ratio minus CRP and used this to calculate sensitivity and specificity cut off points that could pragmatically be used by clinicians ([Figures 1 and 2](#)). Based on these criteria, for patients who concurrently had saturations measured on air and a CRP checked in this cohort ($n=35$), 10 patients would be discharged (five actually discharged), 21 patients would be observed (four actually discharged) and 4 directly admitted (two actually discharged) to hospital.

In a supplementary analysis, we re-examined factors that predicted mechanical ventilation as per our previous publication.⁵ The rationale for this was to include the new CXR and qSOFA scores. Both the CXR score ($P=0.001$) and qSOFA ($P<0.001$) scores were significantly associated with need for ventilation on univariate analysis. CRP was not associated with need for mechanical ventilation ($P=0.236$). On multivariate analysis association with CXR score was not significant, leaving only estimated P/F ratio and qSOFA and independently associated with mechanical ventilation ([Table 4](#)). A receiver operator curve was constructed for this model and demonstrated an area under the curve of 0.939 ([Figure 3](#)).

Conclusions

This study demonstrates that normal oxygen exchange (estimated P/F ratio) and low C-reactive protein levels predict safe discharge for patients who presented to hospital with influenza A (H1N1). Patients safely discharged were also younger, had

Table 1. Patient triage scores and outcome data

	Discharged (n=16)	Admitted (n=70)	<i>P</i> value
qSOFA	0 (0–1)	1 (0–1)	0.009
STSS	0 (0–1)	1 (0–2)	0.003
SOFA	1 (0–2)	2 (1–4)	<0.001
CXR score	1 (1–2)	2 (1–4)	0.003

Patient triage scores: qSOFA, 'quick' sequential organ failure assessment; SOFA, sequential organ failure assessment; STSS, simplified triage severity score. Data displayed as median (IQR) and *p* values calculated by Mann-Whitney *U* analysis.

Table 2. Univariate logistical regression analyses to determine association between clinical factors and safe discharge

Independent variable	Coefficient	Standard error	<i>P</i> values	Pseudo R ²
Age	−0.04	0.02	0.035	0.062
CRP	−0.03	0.01	0.014	0.251
Albumin	0.17	0.07	0.013	0.131
Estimated P/F ratio	0.01	0.01	0.026	0.131
qSOFA	−1.37	0.57	0.016	0.100
STSS	−1.08	0.40	0.006	0.127
CXR score	−0.99	0.39	0.011	0.146

Table demonstrates the relationship between measured clinical variables and subsequent safe discharge. CRP, C-reactive protein; P/F, PaO₂ divided by FiO₂; qSOFA, quick sequential organ failure assessment; STSS, Simplified Triage Severity Score; CXR, chest X-ray.

Table 3. Multivariate logistic regression model to determine association between clinical factors and safe discharge

	Std. coef.	Standard error	<i>P</i> values	95% CI
CRP	−0.03	0.01	0.028	−0.06 to −0.00
Estimated P/F	0.01	0.01	0.056	−0.00 to 0.03

Table displays the output from a multivariate regression analysis constructed by backwards elimination ($P<0.1$) using univariate factors that were significantly associated with safe discharge. Albumin ($\beta=-0.04$, $P=0.682$), the Simplified Triage Severity Score ($\beta=-0.15$, $P=0.861$), quick sequential organ failure assessment score ($\beta=-0.54$, $P=0.556$), chest C-ray score ($\beta=-0.95$, $P=0.139$) and age ($\beta=-0.06$, $P=0.115$) were sequentially eliminated from the model as non-significant. Final model: $n=62$, $\chi^2=21.86$, $R^2=0.359$. Std. coef., standardised coefficient (β value); 95% CI, 95% confidence interval.

higher albumin levels, less deranged physiological scores (qSOFA, SOFA and STSS) and less infiltrates on a quantitative chest X-ray score. Based on our results, we propose a pragmatic triage tool to guide hospital admission and discharge decisions in the event of a future influenza pandemic. This tool requires validation in an additional patient cohort prior to implementation, but these initial results suggest up to one-fifth of the admissions for H1N1 in 2010–11 could potentially have been avoided (1759 of 8797²⁰).

This investigation was conducted on an established patient database previously used to develop a triage tool to predict need for mechanical ventilation.⁵ This database was supplemented to include additional clinical information commonly requested by clinicians treating patients at presentation (CXR) and the qSOFA score in light of the recent update to sepsis definitions.¹⁵ Multiple clinical parameters were associated with safe discharge on univariate analysis ([Table 2](#)) but only estimated P/F ratio and CRP remained as independently associated when a multivariate model was constructed ([Table 3](#)). Our aim was to

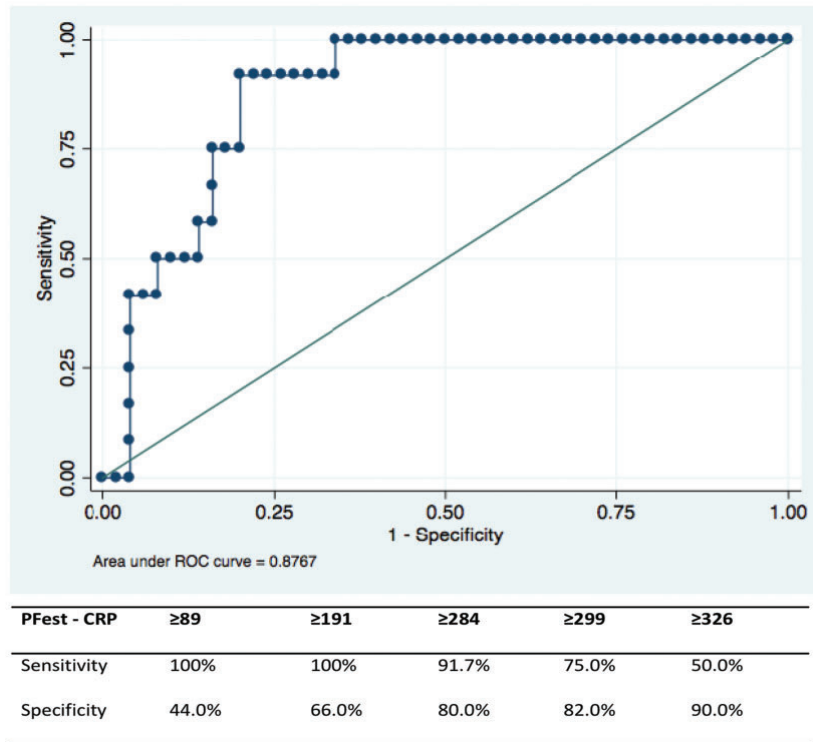


Figure 1. Receiver operator characteristic curve for univariate estimated PaO₂/FiO₂ ratio minus CRP for prediction of discharge. Figure demonstrates a receiver operator curve with area under the curve analysis for the variable estimated PaO₂/FiO₂ minus C-reactive protein in predicting safe discharge. The table below demonstrates specific cut off points for this variable with sensitivity and specificity calculations.

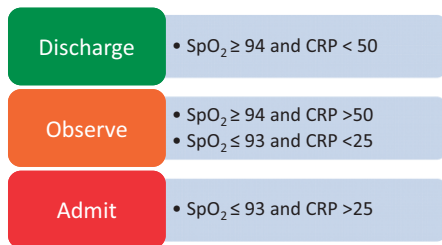


Figure 2. Pragmatic admission and discharge decision-making tool derived using the safe discharge prediction model: estimated PaO₂/FiO₂ ratio minus CRP. Figure demonstrates thresholds for admission, observe (defer decision after 24 h observation period) and direct hospital admission based on our prediction model. Estimated P/F ratio was calculated with saturations on air based on the equation: $\text{Log(PF)} = 0.48 + 0.78 \times \text{Log(SF)}$.¹⁶ Discharge decision = estimated P/F minus CRP ≥ 300. Admit decision = estimated P/F minus CRP ≤ 300.

develop a pragmatic triage tool that can be used by treating clinicians without recourse to complex calculations. Therefore, we constructed a new variable: estimated P/F ratio minus CRP (no weighting) and sensitivity/specificity cut-off points were described (Figure 1). Using this information, we developed a triage tool to guide clinical decision-making that did not require the user to be familiar with calculation of P/F ratio and did not require arithmetic that could introduce error (Figure 2). Estimated P/F ratio was calculated using air (FiO₂ = 0.21) for this tool on the assumption that any patient who requires oxygen to maintain SpO₂ > 93% would automatically require hospital admission. This approach is in line with the British Thoracic

Table 4. Multivariate logistic regression model to determine association between clinical factors and need for mechanical ventilation

	Std. Coef.	Standard error	P values	95% CI
qSOFA	2.11	0.73	0.004	0.68–3.54
Estimated P/F	−0.01	0.00	0.015	−0.02 to −0.00

Table displays the output from a multivariate regression analysis constructed by backwards elimination ($P < 0.1$) using univariate factors that were significantly associated with mechanical ventilation. The chest X-ray score (beta 0.36, $P = 0.303$) was eliminated from the model as non-significant. Final model: $n = 85$, $\chi^2 = 35.03$, $R^2 = 0.461$. Std. coef., standardised coefficient (beta value); 95% CI, 95% confidence interval.

Society guideline on supplemental oxygen stating that oxygen should be titrated to saturations of 94–98% in the emergency setting.²¹

Patients with influenza may rapidly deteriorate within a 24 h period.²² We have, therefore, been conservative in our approach and advocated a period of observation for patients with discordant saturations and CRP before a final admission decision is made (Figure 2). We would caveat our proposed approach to allow factors such as co-morbidity, pregnancy and clinical concern to be incorporated into the final hospital admission decision. Point of care tests are increasingly used by primary care practitioners to measure CRP²³ as recommended by NICE guidelines for the diagnosis and treatment of pneumonia (2014, CG191). Potentially and with future validation, our proposed tool could be used by GPs to guide referral decisions to hospital during a future pandemic.

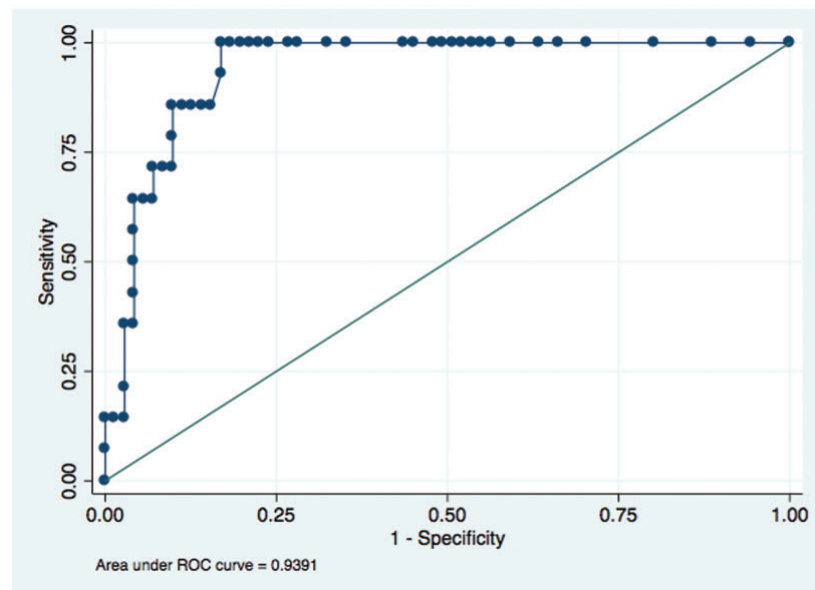


Figure 3. Receiver operator characteristic curve for multivariate model $\text{PaO}_2/\text{FiO}_2$ ratio and qSOFA in predicting need for mechanical ventilation. Figure demonstrates a receiver operator curve with area-under-the-curve analysis for the variable estimated $\text{PaO}_2/\text{FiO}_2$ ratio and qSOFA (quick sequential organ failure assessment score) in predicting safe discharge.

Intuitively, using both an inflammatory marker and oxygen exchange to predict safe discharge is clinically coherent – the H1N1 influenza virus characteristically caused an inflammatory disorder that negatively impacted on oxygen exchange.²⁴ Compared with our previous work,⁵ we found that the discriminatory power of estimated P/F ratio was decreased in patients with near normal oxygen saturations (area under the curve estimated P/F in isolation was 0.653). When CRP was used as the sole predictor of safe discharge in this dataset, the area under the curve was 0.805. The combination of CRP and estimated P/F increased the discriminatory ability of the model (Figure 1).

A number of other potential triage tools have been postulated for pandemic influenza. There has been focus on the impact of pandemic influenza and critical care capacity with assessments of CURB-65, the Simplified Triage Severity Score and the Ontario Health Plan for an Influenza Epidemic; all found to be unreliable predictors of need for critical care admission.^{5–8} Our previous publication highlighted that oxygen exchange was the best predictor of need for mechanical ventilation and admission to critical care.⁵ An alternative investigatory approach has been to identify clinical factors that are associated with a confirmed (PCR +ve) diagnosis of influenza.^{9–13} However, there is a paucity of work that examines hospital admission and discharge decisions for patients with H1N1 influenza. We believe that our proposed tool provides a pragmatic method for incorporating measures of inflammation and oxygen exchange into hospital admission decisions. Clearly this tool requires refinement and validation through study in other cohorts of patients prior to implementation.

Re-examining the need for mechanical ventilation, we investigated qSOFA and Chest X-ray score as supplementary variables. As a part of the recent update on sepsis definition, qSOFA has been advocated as a simple bedside score to identify patients suspected of infection at risk of poor outcome.¹⁵ This score does not require laboratory tests, can be assessed rapidly and repeatedly and, as a surrogate for increased SOFA score

(≥ 2), is associated with a mortality of at least 10%. We applied this tool to our cohort and found that qSOFA increased the discriminatory power of oxygen exchange in predicting the need for mechanical ventilation (area under the curve 0.939). This could be very useful for critical care clinicians to rapidly assess patients who present acutely to hospital.

Eighty-six patients were included, of whom 16 were safely discharged home after initial presentation. This is a relatively small cohort of patients with confirmed H1N1 influenza but other patients with alternative diagnoses were excluded. We recommend that validation and refinement of this tool be conducted before future implementation.

In summary, we have demonstrated that estimated $\text{PaO}_2/\text{FiO}_2$, a measure of lung oxygen exchange, and C-reactive protein accurately predict safe discharge for patients who presented acutely to hospital with pandemic H1N1 influenza. We propose a pragmatic triage tool to guide clinical decision-making that also has the potential to be used in future by primary care physicians when assessing patients in the community. This tool requires validation in a further cohort of patients before potential implementation.

Supplementary material

Supplementary material is available at QJMED online.

Conflict of interest: None declared.

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