ORIGINAL ARTICLE

Risk factors and early prediction of clinical deterioration and mortality in adult COVID-19 inpatients: an Australian tertiary hospital experience

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Abstract

Background: Early recognition of severe COVID-19 is essential for timely patient triage.

Aims: To report clinical and laboratory findings and patient outcomes at a tertiary hospital in Melbourne, Australia.

Methods: This is a retrospective study of adult inpatients with COVID-19 admitted to Northern Health from March to September 2020. Data were extracted from electronic medical records.

Results: Key admission data were available for 182 patients (median age 67.0 years (interquartile range, 47.9–83.1); 51.1% female). Fifty-six (30.8%) were from residential care. One hundred and seventeen (64.3%) patients were assigned Goals of Patient Care (GOPC) A or B and 65 (35.7%) GOPC C or D. Comorbidities were present in 135 patients (74.2%). 63.2% of patients received antibiotics, 6.6% had antivirals, 45.6% received systemic glucocorticoid and 3.3% had tocilizumab. Fifty-six (30.8%) developed clinical deterioration (24 requiring ventilation, 21 receiving critical care, 34 died). Overall, inhospital clinical deterioration was significantly associated with older age ($P < 0.001$), history of diabetes ($P = 0.038$), lower lymphocyte count ($P = 0.002$) and platelet count ($P = 0.004$), higher neutrophil-to-lymphocyte ratio ($P = 0.002$), elevated fibrinogen ($P = 0.004$), higher serum ferritin ($P = 0.027$) and C-reactive protein (CRP; $P = 0.002$). The accuracy of the 4C Deterioration model was moderate, with an area under the curve (AUC) of 0.79 (95% confidence interval (CI), 0.68–0.90) compared with an AUC of 0.77 (95% CI, 0.76–0.78) in the original validation cohort.

Conclusions: In the present study, high neutrophil-to-lymphocyte ratio, abnormal D-dimer, high serum CRP and ferritin appear to be useful prognostic markers.

Introduction

Since late 2019, the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been exponential, resulting in a global pandemic with more than 168 million confirmed cases to date (as of 5 May 2021) and over 3.4 million deaths.[1] Older people, particularly those with comorbidities, such as hypertension, diabetes mellitus and chronic obstructive pulmonary disease, are more likely to develop serious disease.[2] One of the

challenges clinicians currently face is the lack of verified data or risk stratification scores to predict disease severity and identify patients with a high risk of requiring ventilation and/or intensive care.[3]

Routine laboratory measures play an important role in COVID-19 patient care. Marked coagulopathy is a key feature of SARS-CoV-2 infection with elevated D-dimer and thrombocytopenia consistently associated with unfavourable disease progression.[4,5] Lymphopenia and the magnitude of lymphocyte count reduction is also associated with disease severity along with an elevated neutrophil-to-lymphocyte ratio.[6,7] In terms of biochemical parameters, increased serum C-reactive protein

(CRP) concentration and serum ferritin have consistently been shown to be associated with poor outcome in SARS-CoV-2 infection.[8] As a non-specific marker of tissue damage, plasma lactate dehydrogenase (LDH) emerges as one of the most consistently elevated markers in COVID-19 patients at higher risk of developing an adverse outcome.[9]

While the rate of COVID-19 cases in Australia is lower than in other countries, early and effective triage for risk of deterioration is important for clinical decision-making and to facilitate hospital resource distribution.[3] Numerous multivariable prognostic models for patients with COVID-19 have been developed to predict clinical deterioration. A key prognostic model that has been developed and validated is the 4C Deterioration model, which reported C-statistic of 0.77 indicating ability to discriminate at hospital admission between patients likely and unlikely to deteriorate.[3] Predictors include demographic, comorbidities and laboratory test variables (Supporting Information Table S1).[3] Another notable prediction tool was developed by Zhang and colleagues based on data from Wuhan (China), using logistic regression with poor outcome and death as outcomes – the DL-Poor and DL-Death models – which performed well in internal validation in the lower-risk derivation population (China), but less well in the much higher-risk external validation population (UK).[10]

We performed a retrospective audit of the COVID-19 patients admitted to Northern Health to identify the key clinical characteristics and laboratory parameters associated with patient deterioration. Northern Health is a tertiary health service that cares for a diverse community, born in more than 185 countries. Two prediction tools for clinical deterioration (4C Deterioration and DL-Poor) and the widely used quick Sequential Organ Failure Assessment (qSOFA) score were also retrospectively applied to the COVID-19 inpatient cohort, to assess their applicability in the local multi-ethnic population.[3,10,11]

Methods

All patients with confirmed COVID-19 infection admitted to Northern Health from March to September 2020 (when Victoria experienced the first and second waves of COVID-19) were included. Patients were identified through the hospital reporting portal, medical records (based on International Classification of Diseases (ICD-10) coding) and laboratory information system (based on positive SARS-CoV-2 nucleic acid test results performed using real-time reverse transcription–polymerase chain reaction methods). The laboratory parameters of the first requested blood tests from the time of swab or hospital admission were recorded.

Hospital admission records were retrospectively reviewed with data collected, including patient demographics, goals of patient care (GOPC), medical comorbidities, treatments, clinical course and patient outcomes. There were four GOPC categories: Goal A identifies patients without treatment limitations for whom cardiopulmonary resuscitation (CPR) would apply; Goal B, those for whom some treatment limitations apply, including not for attempted CPR but for intubation; Goal C, for whom investigations or treatment should only be undertaken if non-burdensome; and Goal D identifies patients who are in the terminal stage of illness for whom all interventions should be for comfort only.[12]

From the total cohort of COVID-19 inpatients, we selected patients who had complete data for calculating their 4C Deterioration and DL-Poor scores (Table S1). Similar to the studies that originally validated the prediction tools, we defined inhospital clinical deterioration as initiation of ventilatory support, admission to an intensive care unit (ICU) or death. This aligns closely with a score of 6 or higher on the WHO Clinical Progression Scale and ensures that the clinical outcome is harmonised across hospitals.[3,13] The qSOFA score was assessed for its accuracy in predicting mortality.[11] The score uses three criteria, assigning one point for low blood pressure (systolic blood pressure ≤100 mmHg), high respiratory rate (≥22 breaths per min) or altered mental state (Glasgow coma scale <15).[13] The presence of two or more qSOFA points near the onset of infection was associated with a greater risk of death or prolonged ICU stay.[11]

Statistical analysis

Continuous and categorical variables were presented as median (interquartile range, IQR) and n (%) respectively. Mann–Whitney U-test, χ^2 test or Fisher's exact test was used to compare differences in variables between the patient groups (with and without clinical deterioration). To explore risk factors associated with inhospital clinical deterioration and death, univariate logistic regression model was used.

In validating prediction tools, we classified patients by quintile of predicted risk for critical illness based on clinical deterioration score and compared the observed outcomes with the predicted outcomes using the χ^2 test. Accuracy in the sample was tested by measuring area under the receiver operating characteristic curve (AUC). Data analyses were performed using the Analyse-it v5.65.7 add-in package (Analyse-it Software Ltd, Leeds, UK) for Microsoft Excel. P-values were two-tailed and statistical significance was defined as P-value <0.05.

Table 1 Demographic, clinical, laboratory and radiographic findings of all patients (GOPC A/B/C/D) on hospital admission and outcome (clinical deterioration vs no deterioration)

Characteristic	Total (*n* = 182)	No deterioration (*n* = 126)	Deterioration (*n* = 56)	*P*-value	Univariable OR (95% CI)
Demographics and clinical characteristics					
Age (years)	67.0 (47.9–83.1)	62.5 (42.9–79.0)	76.0 (58.3–88.0)	**0.0005**	
Sex				**0.0377**	1.995 (1.052–3.780)
Female	93 (51.1%)	71 (56.3%)	22 (39.3%)		
Male	89 (48.9%)	55 (43.7%)	34 (60.7%)		
Current smoker	8 (4.4%)	7 (5.6%)	1 (1.8%)		
Hypertension	104 (57.1%)	66 (52.4%)	38 (67.9%)	0.0540	
Diabetes	55 (30.2%)	32 (25.4%)	23 (41.1%)	**0.0375**	2.047 (1.054–3.981)
Coronary heart disease	28 (15.4%)	18 (14.3%)	10 (17.9%)	0.6565	
Chronic obstructive lung disease	10 (5.5%)	4 (3.2%)	6 (10.7%)	0.0708	
Carcinoma	2 (1.1%)	1 (0.8%)	1 (1.8%)	0.5219	
Chronic kidney disease	18 (9.9%)	12 (9.5%)	6 (10.7%)	0.7926	
Glasgow coma score (GCS) <15	52 (28.6%)	25 (19.8%)	27 (48.2%)	**0.0002**	3.761 (1.904–7.432)
Respiratory rate ≥22 breaths per min	57 (31.3%)	29 (23.0%)	28 (50.0%)	1.0000	
Systolic blood pressure <100 mmHg	17 (9.3%)	10 (7.9%)	7 (12.5%)	1.0000	
qSOFA score (2–3)	23 (12.6%)	8 (6.3%)	15 (26.8%)	0.2525	
	n = 116	*n* = 89	*n* = 27		
Weight ≥100 kg	24 (20.7%)	16 (18.0%)	8 (29.6%)	0.2765	
	n = 182	*n* = 126	*n* = 56		
Laboratory findings					
White blood cell count (×10⁹ per L)					
≤4	42 (23.1%)	31 (24.6%)	11 (19.6%)	0.7066†	
5–9	106 (58.2%)	71 (56.3%)	35 (62.5%)		
≥10	34 (18.7%)	24 (19.0%)	10 (17.9%)		
Lymphocyte count (×10⁹ per L)	1.00 (0.70–1.41)	1.00 (0.80–0.60)	0.80 (0.60–1.10)	**0.0015**	
Neutrophil	4.40 (3.00–6.20)	4.20 (2.99–6.10)	5.25 (3.38–6.42)	0.1653	
Neutrophil-to-lymphocyte ratio	4.00 (2.44–7.22)	3.50 (2.21–6.51)	5.55 (3.42–8.85)	**0.0023**	
Platelet count (×10⁹ per L)	221.0 (175.9–273.0)	232.5 (185.0–279.0)	194.5 (161.3–243.5)	**0.0040**	
Platelet <100	3 (1.6%)	2 (1.6%)	1 (1.8%)	1.0000	
Platelet-to-lymphocyte ratio	205.6 (151.0–303.6)	196.8 (149.7–293.4)	235.6 (158.8–331.1)	0.0878	
Haemoglobin (g/L)	133.0 (119.9–148.0)	134.0 (120.0–148.0)	127.5 (116.7–147.0)	0.4086	
CRP (mg/L)	51.5 (13.0–99.0)	37.5 (12.0–85.0)	76.5 (34.0–126.2)	**0.0004**	
CRP >40	102 (56.0%)	61 (48.4%)	41 (73.2%)	**0.0021**	2.913 (1.471–5.761)
	n = 130	*n* = 93	*n* = 37		
LDH (U/L)	287.5 (212.7–360.1)	278.0 (197.3–332.3)	336.0 (276.0–466.3)	**0.0015**	
LDH >250	85 (65.4%)	54 (58.1%)	31 (83.8%)	**0.0074**	3.731 (1.445–9.580)
	n = 146	*n* = 102	*n* = 44		
Ferritin (μg/L)	328.0 (168.4–816.3)	310.5 (151.9–620.3)	568.0 (174.9–1855.0)	**0.0267**	
>300	79 (54.1%)	52 (51.0%)	27 (61.4%)	0.2807	
	n = 148	*n* = 103	*n* = 45		
D-dimer (mg/L FEU)	0.69 (0.44–1.16)	0.65 (0.42–1.10)	0.80 (0.55–1.90)	0.0632	
<0.5	37 (25.0%)	30 (29.1%)	7 (15.6%)	0.0995	
≥0.5	111 (75.0%)	73 (70.9%)	38 (84.4%)		
	n = 125	*n* = 84	*n* = 41		
Fibrinogen (g/L)	5.20 (4.20–6.42)	4.99 (4.00–6.06)	6.10 (4.84–6.83)	**0.0028**	
≤4.0	24	22	2	**0.0036**	2.231 (0.910–5.443)
>4.0	101	62	39		
	n = 81	*n* = 56	*n* = 25		

Table 1 *Continued*

Characteristic	Total (*n* = 182)	No deterioration (*n* = 126)	Deterioration (*n* = 56)	*P*-value	Univariable OR (95% CI)
High-sensitivity troponin I ≥26 ng/L		8 (14.3%)	9 (36%)	**0.0266**	3.375 (1.135–10.056)
	n = **173**	*n* = **118)**	*n* = **55**		
Imaging changes	96 (55.5%)	56 (47.5%)	40 (72.7%)	**0.0019**	2.952 (1.479–5.886)
Consolidation	79 (45.7%)	49 (41.5%)	30 (54.5%)	0.1005	
Ground-glass opacity	20 (11.6%)	10 (8.5%)	10 (18.2%)	0.0729	
Bilateral pulmonary infiltration	7 (4.0%)	2 (1.7%)	5 (9.1%)	**0.0321**	5.918 (1.266–27.403)

†χ^2 test comparing all subcategories.

Data are median (IQR), *n* (%) or *n/N* (%). *P*-values were calculated using Mann–Whitney *U*-test, χ^2 test or Fisher's exact test, as appropriate. *P*-value of <0.05 was considered signficant (values in bold). Deterioration is defined as requiring ventilatory support, critical care or patient death.

CI, confidence interval; CRP, C-reactive protein; GOPC, Goals of Patient Care; LDH, lactate dehydrogenase; OR, odds ratio; qSOFA, quick Sequential Organ Failure Assessment.

The research was conducted according to the principles of the Declaration of Helsinki. The Northern Health Office of Research approved the study as a quality improvement audit (ALR 69.2020).

Results

A total of 1284 COVID-19 positive cases was diagnosed through Northern Health's pathology department between March and October 2020. Of these, 195 adults were hospitalised in Northern Health with COVID-19. Key clinical and laboratory data were available for 182 patients (Table 1). The median age of the 182 patients was 67.0 years (IQR, 47.9–83.1; range, 18–98 years) and 93 (51.1%) patients were female. Of the 182 patients, 56 (30.8%) of them were from residential care. A total of 117 (64.3%) patients was assigned to GOPC A or B and 65 (35.7%) patients GOPC C or D. Comorbidities were present in more than half (*n* = 135) of patients, with hypertension (57.1%) being the most common, followed by diabetes (30.2%), weight ≥100 kg (only 20.7% of 116 patients with weight recorded) and coronary heart disease (15.4%). Patients assigned GOPC C/D were older (median 85.0 (IQR 78.7–90.0) vs median 54.0 (IQR 40.7–65.3); *P* < 0.001), more likely to be from residential care (81.5% vs 2.6%; *P* < 0.001) and more likely to have medical comorbidities (56.4% vs 86.2%; *P* < 0.001).

Overall, a total of 115 (63.2%) patients received antibiotics and 12 (6.6%) antivirals. Systemic glucocorticoid was used in 83 (45.6%) patients and tocilizumab in 6 (3.3%) individuals. There were 25 patients who were on therapeutic anticoagulation prior to and during admission while 134 patients were commenced on prophylactic anticoagulation and three on intermediate dose. There were only four (2.2%) cases of venous thromboembolism reported. No patient received convalescent plasma. A total of 56 (30.8%) patients developed clinical deterioration (24 required ventilation, 21 admitted to the ICU, 34 died). There was only one (0.8%) death in the GOPC A/B patient cohort compared with 29 (46.8%) deaths in patients with GOPC C (*P* < 0.001). All patients with GOPC D were admitted for palliative care and all succumbed. Patients designated as GOPC C or D had a significantly higher mortality rate (OR, 119.63 (95% confidence interval (CI), 19.69–714.67)).

In the univariate logistic analysis of all 182 patients, inhospital clinical deterioration was significantly associated with older age (*P* < 0.001), history of diabetes (*P* = 0.038), lower lymphocyte count (*P* = 0.002), higher neutrophil-to-lymphocyte ratio (*P* = 0.002), lower platelet count (*P* = 0.004), fibrinogen >4.0 g/L (*P* = 0.004), higher serum ferritin (*P* = 0.027), high sensitivity cardiac troponin I ≥26 ng/L (*P* = 0.0266) (the cut-off of 26 ng/L was chosen as it is the overall population 99th percentile) and CRP concentrations >40 mg/L (*P* = 0.002; Table 1).

In a subanalysis of patients with GOPC A/B (*n* = 117), inhospital clinical deterioration was associated with weight ≥100 kg (in the 83 patients with weight recorded) although there did not appear to be an association with other underlying comorbidities (Table 2). Clinical deterioration was also significantly associated with tachypnoea (respiratory rate ≥22 breaths per min), CRP >40 mg/L, elevated serum LDH, as well as those with ground-glass opacity and bilateral pulmonary infiltration on chest imaging. Interestingly, lymphocyte and platelet counts were not associated with clinical deterioration in this subgroup. Patients with lower fibrinogen and abnormal D-dimer (≥0.5 mg/L FEU) were more likely to have clinical deterioration (*P* = 0.0233). A qSOFA score of 2–3 was associated with increased risk of mortality in our COVID-19 inpatient cohort (*P* < 0.0001). There were 20 deaths in patients with qSOFA 0–1 (20/159, 12.6%)

Table 2 Demographic, clinical, laboratory and radiographic findings of patients with GOPC A or B on hospital admission and outcome (clinical deterioration vs no deterioration)

Characteristic	GOPC A/B	GOPC A/B	GOPC A/B	P-value	Univariable OR (95% CI)
	Total (n = 117)	No deterioration (n = 94)	Deterioration (n = 23)		
Demographics and clinical characteristics					
Age (years)	54.0 (40.7–65.3)	53.5 (40.0–66.1)	54.0 (47.3–64.8)	0.6286	
Sex				0.1658	
Female	57 (48.7%)	49 (52.1%)	8 (34.8%)		
Male	60 (51.3%)	40 (42.6%)	15 (65.2%)		
Current smoker	7 (6.0%)	6 (6.4%)	1 (4.3%)		
Hypertension	56 (47.9%)	44 (46.8%)	12 (52.2%)	0.6508	
Diabetes	32 (27.4%)	22 (23.4%)	10 (43.5%)	0.0685	
Coronary heart disease	11 (9.4%)	10 (10.6%)	1 (4.3%)	0.6898	
Chronic obstructive lung disease	3 (2.6%)	3 (3.2%)	0 (0.0%)	1.0000	
Carcinoma	2 (1.7%)	1 (1.1%)	1 (4.3%)	0.3559	
Chronic kidney disease	6 (5.1%)	6 (6.4%)	0 (0.0%)	0.5963	
Glasgow coma score (GCS) <15	5 (4.3%)	5 (4.3%)	0 (0.0%)	0.5814	
Respiratory rate ≥22 breaths per min	58 (49.6%)	42 (44.7%)	16 (69.6%)	**0.0381**	2.830 (1.083–7.361)
Systolic blood pressure <100 mmHg	7 (6.0%)	6 (6.4%)	1 (4.3%)	1.0000	
qSOFA score (2–3)	7 (6.0%)	6 (6.4%)	1 (4.3%)	1.0000	
	n = 83	*n = 68*	*n = 15*		
Weight ≥100 kg	20 (24.1%)	13 (19.1%)	7 (46.7%)	**0.0239**	3.702 (1.168–11.830)
	n = 117	*n = 94*	*n = 23*		
Laboratory findings					
White blood cell count (×10⁹ per L)					
≤4	30 (25.6%)	25 (26.6%)	5 (21.7%)	0.8918†	
5–9	63 (53.8%)	50 (53.2%)	13 (56.5%)		
≥10	24 (20.5%)	19 (20.2%)	5 (21.7%)		
Lymphocyte count (×10⁹ per L)	1.00 (0.80–1.43)	1.00 (0.80–1.60)	0.90 (0.72–1.10)	0.1241	
Lymphocyte <0.8	26 (22.2%)	20 (21.3%)	6 (26.1%)	0.6189	
Neutrophil		4.00 (2.89–6.10)	4.40 (3.53–6.87)	0.3743	
Neutrophil-to-lymphocyte ratio	3.89 (2.39–6.54)	3.50 (2.21–6.51)	4.88 (2.80–8.06)	0.1070	
Platelet-to-lymphocyte ratio	205.0 (150.9–294.4)	193.1 (150.7–307.7)	235.0 (162.4–279.4)	0.3856	
Haemoglobin (g/L)	139.0 (125.0–150.0)	136.5 (122.9–150.0)	143.0 (126.2–153.2)	0.4261	
Platelet count (×10⁹ per L)	233.0 (183.7–279.7)	234.0 (184.9–281.2)	225.0 (168.7–250.7)	0.3581	
Platelet <100	2 (1.7%)	2 (2.1%)	0 (0.0%)	0.4804	
CRP (mg/L)	49.5 (14.0–92.7)	33.5 (10.0–84.1)	96.0 (55.0–132.0)	**0.0001**	
CRP >40	65	45	20	**0.0007**	7.589 (2.127–24.460)
	n = 94	*n = 73*	*n = 21*		
LDH (U/L)	285.0 (208.4–371.6)	278.0 (195.7–333.3)	371.0 (282.0–558.0)	**0.0014**	
LDH >250	61 (64.9%)	43 (58.9%)	18 (85.7%)	**0.0233**	4.186 (1.189–14.505)
	n = 101	*n = 79*	*n = 22*		
Ferritin (µg/L)	329.0 (166.7–933.7)	295.0 (141.5–703.8)	821.5 (230.0–2498.4)	**0.0022**	
>300	55 (54.5%)	39 (49.4%)	16 (72.7%)	0.0517	
	n = 100	*n = 77*	*n = 23*		
D-dimer (mg/L FEU)	0.57 (0.40–0.99)	0.53 (0.38–0.81)	0.80 (0.56–1.10)	**0.0183**	
<0.5	33 (33.0%)	30 (39.0%)	3 (13.0%)	**0.0233**	
≥0.5	67 (67.0%)	47 (61.0%)	20 (87.0%)		
	n = 83	*n = 60*	*n = 23*		

Table 2 *Continued*

Characteristic	GOPC A/B	GOPC A/B	GOPC A/B	P-value	Univariable OR (95% CI)
	Total (n = 117)	No deterioration (n = 94)	Deterioration (n = 23)		
Fibrinogen (g/L)	5.30 (4.70–6.70)	5.20 (4.24–6.37)	6.40 (5.34–7.05)	**0.0042**	
≤4.0	13	13	0	**0.0157**	
>4.0	70	47	23		
	n = 62	n = 50	n = 12		
High-sensitivity troponin I ≥26 ng/L	6 (9.7%)	5 (10%)	1 (8.3%)	1.0000	
	n = 112	n = 89	n = 23		
Imaging features	62	43	19	**0.0042**	5.081 (1.655–15.447)
Consolidation	50	37	13	0.1575	2.030 (0.796–5.165)
Ground-glass opacity	14	8	6	**0.0316**	3.797 (1.200–12.109)
Bilateral pulmonary infiltration	6	2	4	**0.0137**	9.667 (1.884–48.873)

†χ^2 test comparing all subcategories.
Data are median (IQR), n (%) or n/N (%). P-values were calculated using Mann–Whitney U-test, χ^2 test or Fisher's exact test, as appropriate. P-value of <0.05 was considered signficant (values in bold). Deterioration is defined as requiring ventilatory support, critical care or patient death.
CI, confidence interval; CRP, C-reactive protein; GOPC, Goals of Patient Care; LDH, lactate dehydrogenase; OR, odds ratio; qSOFA, quick Sequential Organ Failure Assessment.

compared to 14 in the group with qSOFA 2–3 (14/23, 60.9%; univariable OR 10.8 (95% CI 4.2–27.8)).

Complete data were available for calculation of the 4C Deterioration and DL scores for 168 patients. The accuracy of the 4C Deterioration tool in our patient cohort was moderate, with an AUC of 0.83 (95% CI, 0.77–0.90) compared with an AUC of 0.77 (95% CI, 0.77–0.78) in the original UK validation cohort (Fig. 1). The accuracy of the DL-Poor tool in the same patient cohort was similarly moderate, with an AUC of 0.71 (95% CI, 0.59–0.82). When patients in each GOPC category were grouped by probability of

clinical deterioration (<0.4 and ≥0.4) based on the 4C Deterioration model, there was a significant association between the probability of deterioration and GOPC categories (P < 0.0001).

Discussion

The present study provides a real-world overview of an Australian experience of COVID-19 in a tertiary Melbourne hospital at the centre of the second COVID-19 wave in 2020. In our study, in which 30.8% of patients were from residential care, we demonstrated a significant mortality rate (approximately 18%) that impacted predominantly individuals who were older and from residential care, consistent with overseas experience, highlighting the significant impact this disease has on older vulnerable populations.[14]

Our findings of the association of a more severe clinical course with older age, male sex and diabetes agree with previous publications.[15,16] The key laboratory parameters that contributed to clinical deterioration in our cohort included lymphocyte count, serum CRP, LDH and D-dimer, consistent with previous reports from larger studies.[3,5–9] Obesity has been reported as a risk factor for deterioration.[17,18] Of note, in our study, we used weight ≥100 kg as a surrogate marker for obesity because height, and hence the body mass index, was often not recorded in the clinical notes. An individual weight of ≥100 kg was associated with deterioration in the GOPC A and B cohort, although it was not a significant risk factor in the overall cohort. Other comorbidities such as age and frailty might be of greater importance in the GOPC C and D populations.
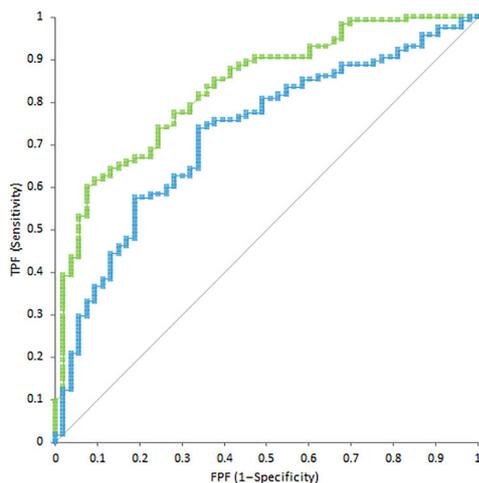

Figure 1 ROC-AUC curves of different models (4C Deterioration and DL-Poor) in predicting clinical deterioration or poor outcome in patients admitted with COVID-19 (n = 168 individuals). (——), No discrimination; (—■—), 4C Deterioration (0.833); (—■—), DL-Poor (0.722). FPF, fale positive fraction; ROC-AUC, receiver operating characteristic curve- area under curve; TPF, true positive fraction.

In the patient cohort with GOPC A and B who were eligible for ventilatory support and/or intensive care, the laboratory parameter with the largest association with clinical deterioration was serum CRP concentration >40 mg/L (OR, 7.589 (95% CI, 2.127–24.460)). Manson and colleagues have defined COVID-19-associated hyper-inflammation (COV-HI), with a serum CRP concentration greater than 150 mg/L, a doubling of CRP concentration within 24 h from a concentration of greater than 50 mg/L or a ferritin concentration of greater than 1500 μg/L.[19] In the UK patient cohort, meeting the COV-HI criteria on admission were associated with higher mortality (40%) than those who did not meet the criteria (26%).[19] Among patients eligible for full escalation of treatment, as high as 37% of them fulfilled the COV-HI criteria at admission, and 62% of these patients required escalation of respiratory support by Day 3.[19] Elevated troponin has been shown by multiple studies to be a predictor of increased mortality risk.[20,21] Sheth *et al.* reported troponin levels were significantly higher in COVID-19 patients who died or were critically ill versus those who survived or not critically ill (WMD 0.57; 95% CI, 0.43–0.70; *P* < 0.001).[22] However, in our study elevated high-sensitivity troponin (a cut-off of 26 ng/L was chosen as it is the overall population 99th percentile) was associated with clinical deterioration in the overall cohort analysis, but not in the GOPC A and B population.

As a biomarker of fibrin formation and degradation, D-dimer is widely reported as a predictive marker of poor clinical outcome in COVID-19 patients.[23–25] In our population receiving active treatment (GOPC A or B), an abnormal D-dimer (≥0.5 mg/L FEU) was seen in 67.0% (67/100), similar to overseas data showing that up to 76% of patients had elevated D-dimer at hospital presentation.[26] Of note, D-dimer ≥0.5 mg/L FEU was associated with clinical deterioration in patients with GOPC A/B (Table 2), but not in the overall cohort (Table 1). A reason might be that only 78.7% (48/61) of patients receiving conservative management (i.e. GOPC C) had D-dimer measured. Fibrinogen, an acute phase reactant, has been found to be elevated in critically ill COVID-19 patients, similar to what was observed in our cohort particularly those with GOPC A/B.[24] Despite some large cohort studies reporting increased venous thromboembolic complications in COVID-19 patients,[27] these events were only reported in 2.2% of patients in our study. While lymphopenia has previously been reported as a useful prognostic factor in determining clinical course and disease severity in COVID-19,[6,7] we did not find this to be as useful in the patients with GOPC A/B.

Effective clinical management of COVID-19 waves, particularly given impact on hospital resource allocation, requires an accurate assessment of patients' prognosis and reliable predictive models can serve as useful tools. The 4C Deterioration tool was developed overseas to help with patient risk prediction and performed with moderate accuracy in our multi-ethnic COVID-19 inpatients at Northern Health with the 4C Deterioration model having an AUC of 0.83, which is generally considered a good model.[3] As these models involve predictors routinely collected at many hospitals in Australia, they can be combined and included in the standard of care adopted by hospitals to identify better the most appropriate clinical pathways for patients with COVID-19.[3] Nonetheless, other new biomarkers and risk factors will no doubt be identified as we have more experience with this pandemic, and further modification of these risk prediction scores may be required.[3]

This study has several limitations. We acknowledge the potential limitations of the retrospective nature of this study, which is subject to the associated biases and confounders, including treatment selection biases, quality of medical records and the possibility that some individuals may not re-present to our hospitals with post-discharge complications might result in the under-reporting of such complications. The laboratory datasets were collected retrospectively and hence only available data could be analysed, introducing potential bias due to incomplete datasets. In addition, there were no investigation results available from time of symptom onset (only time from hospital presentation), which might limit the applicability of the deterioration score results. Data extraction sought to ensure consistency and accuracy, but was not blinded to outcome.[3] Furthermore, being a single-centre study based in a tertiary hospital setting with limited study numbers, the generalisability of these findings to a wider population is unclear. While we note that ethnicity has been reported as a predictive factor, we were unable to perform a meaningful analysis to examine this as the large majority of patients identified as Australian rather than from their specific ethnic background.[28] Nonetheless, this study provides a clinical overview of an Australian experience of the initial COVID-19 wave and identifies risk factors for poor clinical outcomes.

Conclusion

In summary, our study findings suggest that routine laboratory measures and clinical deterioration prediction models might be useful in predicting a poor outcome in patients admitted with COVID-19 and could support clinicians in patient care. These risk prediction models are likely to undergo further updates as we improve our understanding of COVID-19 and need to be adapted to the differences relating to patient case-mix and care in a local clinical setting.[3] Nonetheless, these scores and their

applicability should be further explored in a prospective manner in our Australian populations.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1 Components of the prediction models for clinical deterioration (4C Deterioration and DL-Poor) and the qSOFA score for mortality.