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Clinical Characteristics and Factors Associated with Severity in Patients Admitted with SARS-CoV-2 Infection

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Abstract

Aims

The aim of this study was to provide an early interval evaluation of laboratory characteristics and clinical outcomes of adult patients with qRT-PCR-confirmed SARS-CoV-2 infection.

Methods

We performed a single-centre retrospective cohort study. All patients with qRT-PCR-confirmed SARS-CoV-2 infection admitted from March 6th to April 2nd were included. Daily laboratory, radiological and clinical parameters were manually collected on every patient.

Results

Forty-six patients were included in the analysis. Thirty-three (72%) of patients were male. The majority of patients (n=33, 89%) had at least one baseline comorbidity. Bilateral consolidation on chest x-ray (n=24, 52%) correlated with level of respiratory support required but not with mortality. Documented fever (n=33, 48%) and hypotension (n=4, 9%) correlated with highest level of respiratory support required. Older age, obesity and more than one baseline comorbid condition were associated with mortality. Regarding laboratory markers, degree of neutrophilia, lymphopenia (n=33, 73%) and raised CRP were significantly associated with death. Raised LDH, ferritin and D-dimer concentrations correlated with degree of oxygen requirement. There was no association between an early PCR cycle quantification (C_q) value (used as a proxy for viral load) and patient outcome.

Conclusions

We found multiple characteristics that correlated with outcome. These findings give an indication as to those patients that are at risk of a poor clinical outcome.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China in late 2019 (Huang et al., 2020). In the following months, multiple countries began to report local epidemics (World Health Organisation, 2020). On the 5th March 2020, a patient was diagnosed with SARS-CoV-2 infection who had been ventilated in the intensive care unit with atypical pneumonia despite having no epidemiological link to a known case or area of high prevalence. This was the first documented community acquisition of SARS-CoV-2 in the Republic of Ireland and was an indication of potential widespread community transmission (Faller et al., 2020).

The aim of this study was to provide an early interval evaluation of laboratory characteristics and clinical outcomes of adult patients admitted with quantitative reverse-transcriptase polymerase-chain-reaction (qRT-PCR) confirmed SARS-CoV-2 infection.

Methods

We performed a single-centre retrospective cohort study. All patients with qRT-PCR confirmed SARS-CoV-2 infection admitted to Cork University Hospital, a large regional teaching hospital in Ireland, from March 6th to April 2nd (twenty-eight days following identification of the first case) were included. Ethics approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC).

Laboratory confirmation of SARS-CoV-2 infection was performed using the MagNA Pure 24/MagNA Pure LC (Roche diagnostics) extraction system and Realstar® (Altona Diagnostics, Hamburg, Germany) or EURORealTime (EUROIMMUN, Lübeck, Germany) SARS-CoV-2 qRT-PCR kits, as per the manufacturer's instructions. Target detection was reported on a LightCycler® 480 Instrument II (Roche) if the quantification cycle (C_q) value was <40. In the absence of assay standardisation with RNA copy number controls, the C_q value was used as a semi-quantitative indication of viral load.

Daily laboratory, radiological and clinical parameters were manually collected on every patient using the data collection tool included in the appendix. Collected data was anonymised and stored on password encrypted files.

Characteristics including age, gender, comorbidities, level of oxygen support, radiological findings, lymphocyte count, neutrophil count, as well as D-Dimer, ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) concentrations were recorded. Patients were followed until discharge or death.

Radiological assessments were either plain x-rays or computed tomography (CT) scans. All findings were reviewed by a consultant radiologist.

Patient characteristics were correlated with clinical outcomes. The primary outcome measured was death. The maximum level of respiratory support required during inpatient stay was documented as a secondary outcome. This was classified as ventilated, requiring non-invasive ventilation (NIV), oxygen-requiring or stable on room air.

Data were analysed using SPSS 26.0. Continuous variables were described as median with the interquartile range, and categorical data were described using frequencies and percentages. Means for continuous variables were compared using the Mann-Whitney or Kruskall-Wallis tests and Bonferroni correction was applied for multiple comparison. The Chi-square test was used to compared categorical data. Univariate analysis was used to evaluate the risk factors associated with death. Values were considered significant if $P<0.05$.

Results

Patient Characteristics

Fifty-one patients who tested positive by qRT-PCR for SARS-CoV-2 were admitted between the 6th March and 2nd April 2020 (28-day period). There were eight patients who tested positive in the community and were referred to hospital by Public Health or Primary Care. Of the fifty-one patients that were positive for SARS-CoV-2, forty-three (84%) were community-acquired cases and the remainder were nosocomial.

Five patients (two male) were admitted with SARS-CoV-2 infection for isolation purposes during the containment phase in-line with public health guidance at the time. All had mild SARS-CoV-2 infection. Observations were stable for all throughout admission with none requiring oxygen support. Laboratory parameters were within normal limits with no lymphopenia (median lymphocyte count 2 $x10^9$/L), or elevation in inflammatory markers observed (median CRP 2 mg/L). All were discharged once the public health strategy transitioned from the containment to the delay phase.

Baseline demographic and clinical data for the remaining forty-six patients are described in Table 1. (Next Page) Laboratory findings are reported in Table 2. Age of patients ranged from 21 to 92 years with a median age of 63 years. Thirty-three patients were male (72%).

Characteristic	Total n = 46	Survived n = 34	Died n = 12	*P* value
Gender				0.299
Male	33 (71.7)	23 (50.0)	10 (21.7)	
Female	13 (28.3)	11 (23.9)	2 (4.3)	
Median age, years (IQR)	63 (51-77)	60 (50-70)	76 (67-82)	0.017
Age Category				0.072
21-30 years	1 (2.2)	1 (2.2)	0 (0)	
31-40 years	2 (4.3)	2 (4.3)	0 (0)	
41-50 years	8 (17.4)	7 (15.2)	1 (2.2)	
51-60 years	8 (17.4)	7 (15.2)	1 (2.2)	
61-70 years	10 (21.7)	9 (19.6)	1 (2.2)	
71-80 years	9 (19.6)	3 (6.5)	6 (13.0)	
81-90 years	7 (15.2)	4 (8.7)	3 (6.5)	
91-100 years	1 (2.2)	1 (2.2)	0 (0)	
Comorbidities	41 (89.1)	30 (65.2)	11 (23.9)	0.743
Hypertension	21 (45.6)	18 (39.1)	3 (6.5)	0.095
Ischaemic heart disease	12 (26.1)	7 (15.2)	5 (10.9)	0.153
Atrial fibrillation	6 (13.0)	2 (4.3)	4 (8.7)	0.015
Other cardiac	10 (21.7)	7 (15.2)	3 (6.5)	0.750
Diabetes mellitus	5 (10.9)	3 (6.5)	2 (4.3)	0.453
Obesity	3 (6.5)	2 (4.3)	1 (2.2)	0.768
Other endocrine	2 (4.3)	2 (4.3)	0 (0)	0.390
Chronic obstructive pulmonary	7 (15.2)	4 (8.7)	3 (6.5)	0.272
disease	9 (19.6)	9 (19.6)	0 (0)	0.047
Asthma	4 (8.7)	2 (4.3)	2 (4.3)	0.254
Other respiratory	2 (4.3)	1 (2.2)	1 (2.2)	0.431
Chronic kidney disease	2 (4.3)	0 (0)	2 (4.3)	0.015
History of stroke	1 (2.2)	0 (0)	1 (2.2)	0.089
Malignancy				

Table 1: Patient demographics and comorbidities. Data are presented as median (interquartile range) and n (% of total). *P*<0.05 was considered significant.

Characteristic	Total n = 46	Survived n = 34	Died n = 12	*P* value
Laboratory values				
Maximum Neutrophils (x10^9/L)	6.1 (4.4-10.3)	5.3 (4.1-7.6)	10.3 (6.5-16.1)	0.007
Not measured	1	1	0	
Minimum Lymphocytes (x10^9/L)	1.50 (0.99-1.76)	0.75 (0.49-1.03)	0.51 (0.33-0.66)	0.038
Not measured	1	1	0	
Lymphopenia (<0.9x10^9/L)	33 (73.3%)	22 (48.9%)	11 (24.4%)	0.094
Not measured	1	1	0	
Maximum CRP (mg/L)	138 (66-209)	115 (47-204)	189 (119-292)	0.049
Not measured	1	1	0	
Maximum LDH (units/L)	659 (502-954)	510 (412-643)	508 (388-746)	0.656
Not measured	6	4	2	
Maximum Ferritin (mcg/L)	661 (327-500)	591 (212-591)	931 (402-1647)	0.524
Not measured	8	6	2	
Maximum D-dimer (mcg/L)	1.02 (0.63-5.39)	0.88 (0.44-2.53)	5.1 (0.71-6.8)	0.071
Not measured	8	7	1	
Raised D-dimer (>0.5 mcg/L)	31 (81.6)	20 (52.6)	11 (28.9)	0.062
Not measured	8	7	1	
Crossing point 1st swab (cycle no.)	23.7 (18.9-28.9)	24.2 (20.5-30.0)	21.9 (17.1-27.5)	0.146
Not available	6	6	0	
Vital Signs on day of admission				
Oxygen saturation (%)	96 (95-98)	96 (95-98)	96 (93-98)	0.291
Respiratory rate (breath/min)	20 (18-24)	20 (18-24)	18 (16-26)	0.575
Systolic BP (mmHg)	123 (113-136)	124 (116-143)	117 (92-132)	0.062
Heart rate (beats/min)	82 (74-89)	84 (75-91)	78 (62-86)	0.124
Temperature (▫C)	36.8 (36.4-37.5)	36.7 (36.4-37.5)	36.9 (36.1-37.4)	0.783
Maximum ventilatory support				0.318
None (room air)	12 (26.1)	11 (23.9)	1 (2.2)	
Nasal prongs or face mask	14 (30.4)	10 (23.9)	4 (8.7)	
High-flow oxygen	8 (17.4)	6 (13.0)	2 (4.3)	
Ventilation	12 (26.1)	7 (15.2)	5 (10.9)	
Radiological findings				0.315
Normal chest x-ray	11 (24.4)	8 (17.4)	3 (6.5)	
Unilateral infiltrate	11 (24.4)	10 (21.7)	1 (2.2)	
Bilateral infiltrates	24 (52.2)	16 (34.8)	8 (17.4)	

Table 2: Patient laboratory data, vital signs, respiratory support and radiological findings. Data are presented as median (interquartile range) and n (% of total). *P*<0.05 was considered significant.

The majority of patients (89.1%, n=41) were classified as having one or more comorbidity. In patients who had a documented comorbidity, hypertension was the most common (45.6%, n=21), followed by ischaemic heart disease (26.1%, n=12). The remaining comorbidities and their associated percentages were as follows: atrial fibrillation (13%), other cardiac (including hypercholesterolaemia and pacemaker in situ) (21%), diabetes (10.9%), obesity (6.5%), chronic obstructive pulmonary disease (15.2%), asthma (19.6%), other respiratory (8.7%), chronic kidney disease (4.3%), history of stroke (4.3%) and current malignancy (2.2%).

Clinical Course and Outcomes

The admission chest x-ray was reported normal in eleven patients (24.4%), unilateral consolidation was reported in eleven patients (24.4%) and bilateral consolidation in twenty-four patients (52.2%). Six patients (13%) underwent CT thorax or CT pulmonary angiogram. Bilateral multifocal ground glass consolidation were reported in five of the six patients (83.3%) who had CT imaging with bilateral nonspecific nodularity reported in the other. One revealed a pulmonary embolism and one had findings consistent with acute respiratory distress syndrome.

Of the patients for whom a lymphocyte count was measured (n=45; 97.8%), thirty-three patients (73.3%) were lymphopenic (lymphocyte count $<0.9 \times 10^9$/L) at some point during their clinical course.

A D-dimer concentration was measured in thirty-eight patients (82.6%) and was raised (>0.5 mg/L) in thirty-one of these patients (81.6%).

Twelve patients (26.1%) did not require any form of oxygen support. Fourteen patients (30.4%) required oxygen therapy via nasal prongs or a venturi mask. Eight patients (17.4%) required NIV with oxygen concentrations ranging from 30-80%. A total of twelve patients (26.1%) required invasive ventilatory support. Of the patients who were ventilated, seven were discharged (58.3%) and five died (41.7%).

Overall mortality was 26.1% (n=12). Amongst the patients with nosocomial-acquired infection, the mortality rate was 50% (n=3). The mortality rate was 23% (n=9)amongst patients with community-acquired infection.

Features associated with severity

Age

Older age significantly correlated with risk of death ($P<0.01$).

Gender

There was no statistically significant correlation between gender and outcome or maximum oxygen or ventilatory support required. Of the twelve deaths that occurred in our patient cohort, ten (83.3%) were male.

Clinical Characteristics

Twenty-two (47.8%) of our cohort had a documented fever (temperature >37.4°C). Presence of a fever correlated with the maximum level of oxygen support required, although this wasn't statistically significant (*P*=0.056).

Four patients (8.7%) had documented hypotension (systolic blood pressure <90 mm Hg). There was a significant correlation between hypotension and maximum level of support required, with one patient requiring high-flow oxygen therapy and three patients requiring mechanical ventilation (*P* <0.05).

Comorbidities

Obesity (defined as BMI >30) was associated with maximum level of ventilatory support required (*P*<0.05) but was not associated with mortality. However, overall number of obese patients in our cohort was low.

There was no association between the presence of hypertension and level of ventilatory support required or outcome.

There was a significant correlation between presence of asthma and survival (*P*<0.05). There was no association between the presence of COPD and level of support required or outcome.

There was a significant correlation between presence of atrial fibrillation and a history of stroke and mortality (*P*<0.05).

Radiological findings

There was a significant correlation between the maximum level of ventilatory support required and a chest x-ray finding of bilateral consolidation (*P*<0.001). Chest x-rays were more likely to have been normal in patients that did not require any oxygen support.

Laboratory parameters

Lower minimum lymphocyte count was associated with greater mortality (*P*<0.05). There was no difference in minimum lymphocyte count between patients that were maintained on room air or those that required any level of oxygen support.

Higher maximum neutrophil was observed in count between who died (*P*<0.01). There was no correlation between neutrophil count and the maximum level of oxygen support required.

The maximum CRP concentration was significantly higher in patients who died (*P*<0.05). It was also higher in patients who required ventilation (*P*<0.001) compared to those that did not require any oxygen support. There was no significant difference between any of the oxygen-requiring groups.

Patients who were ventilated had a significantly higher maximum LDH concentration than patients who did not require oxygen support (P<0.01), patients who required oxygen via nasal prongs or Venturi (P<0.05) and patients who required high flow oxygen therapy (P<0.05). However, maximum LDH did not correlate with death.

Patients who were ventilated had a significantly higher D-dimer concentration compared to patient on room air (P<0.05), on oxygen via nasal prongs or Venturi (P<0.01) or on high-flow oxygen (P<0.01). However, there was no correlation between a raised D-dimer and patient survival.

There was no association between an early C_q value (as a proxy for viral load) and the level of oxygen support required or patient outcome. There was also no association between the C_q value and minimum lymphocyte count.

Discussion

This paper provides an overview of adult patients with SARS-CoV-2 infection admitted during the early stages of the pandemic in the Republic of Ireland.

Overall mortality was high at 26%. This mirrors mortality reported in a large prospective observational study of hospitalised patients (n= 20,133) undertaken in the United Kingdom (Docherty et al., 2020).

A significant proportion of patients in this study required ventilator support (26.1%). This was greater than the proportion who required ventilator support in cohorts reported from the UK (17%;(Docherty et al., 2020), Italy (17%;(Grasselli et al., 2020), New York (14%;(Richardson et al., 2020) and China (Guan et al., 2020; Huang et al., 2020).

Critical care capacity in our centre was not exceeded during the study period. Despite this, over half (58%) of patients who died were not admitted to intensive care, indicating advanced care planning occurred.

Our hospitalised cohort were generally older and predominantly male with high rates of comorbidity consistent with reports from the wider literature (Garg et al., 2020; Myers, Parodi, Escobar, & Liu, 2020).

We found a number of clinical characteristics correlated with outcome. Bilateral infective consolidation on chest x-ray strongly correlated with level of respiratory support required. Fever and hypotension correlated with highest level of support required. Age, obesity and more than one baseline comorbid condition were all associated with mortality. We did not find hypertension to be associated with mortality, however the proportion of patients with diagnosed hypertension in our cohort (45.6%) was high compared with estimated prevalence in the general population (Balanda, Barron, Fahy, & McLaughlin, 2010).

No patients in our cohort with asthma died. Elsewhere in Ireland a 6% (1/17) mortality rate has been reported in patients with asthma admitted with COVID-19 (Butler et al., 2020), also considerably lower than our overall mortality rate. It has been hypothesised that reduced expression of the SARS-CoV-2 receptor ACE2 found in respiratory epithelial cells from children and adults with allergic asthma (Jackson et al., 2020) may be protective against severe disease. It has also been speculated that inhaled corticosteroid therapy may play a role (Halpin, Faner, Sibila, Badia, & Agusti, 2020).

Regarding laboratory characteristics, we found degree of neutrophilia, lymphopenia and raised CRP concentration to be significantly associated with death. Raised LDH, ferritin and D-dimer concentrations were significantly correlated with degree of oxygen requirement. Again this supports findings in the wider literature (Sun et al., 2020).

The lack of correlation between qRT-PCR Cq value and outcome or highest level of oxygen support in our study suggests that degree of viral replication does not relate to disease severity. This is in contrast to a study by Pujadas et al. (2020), in which viral load was found to be an independent predictor of SARS-CoV-2 related mortality(Pujadas et al., 2020)**.** Possible confounders in our study include quality and timing of sampling, as replication in the nasopharynx is thought to peak during the first week of illness, and decline thereafter (Wölfel et al., 2020). In addition, it has been shown that the highest level of morbidity and mortality related to SARS-CoV-2 occurs in the inflammatory phase, which occurs approximately eight days after peak infectivity (Torres Acosta & Singer, 2020; Yang et al., 2020). More detailed quantitative PCR studies would be required to further investigate this hypothesis.

This study has several limitations. It was a retrospective study. The study period was relatively short, and thus overall study number is small, however it was felt that short interval review of cases would be important in informing future assessment and management of cases. Data was collected from a single centre and findings may not be generalizable to all other centres.

Data informing assessment, management and therapeutics for patients with SARS-Co-V-2 infection is emerging and evolving rapidly as the pandemic progresses worldwide. The findings presented may serve as a means to stratify higher risk individuals and give an indication as to those patients that may require a higher level of care. While findings from this study largely reflect those reported in international cohorts, local data will improve our understanding of the clinical characteristics and outcomes of patients with SARS-CoV-2 infection in the Irish context.

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Declaration of Conflicts of Interest:
The authors declare no conflicts of interest.

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