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Hospitalised COVID-19 outcomes are predicted by hypoxaemia and pneumonia phenotype irrespective of the timing of their emergence

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ABSTRACT

Despite the known clinical importance of hypoxemia and pneumonia, there is a paucity of evidence for these variables with respect to risk of mortality and short-term outcomes among those hospitalised with COVID-19.

Objective Describe the prevalence and clinical course of patients hospitalised with COVID-19 based on oxygenation and pneumonia status at presentation and determine the incidence of emergent hypoxaemia or radiographic pneumonia during admission.

Methods A retrospective study was conducted using a Canadian regional registry. Patients were stratified according to hypoxaemia/pneumonia phenotype and prevalence. Clinical parameters were compared between phenotypes using χ^2 and one-way Analysis of variance (ANOVA). Cox analysis estimated adjusted Hazard Ratios (HR) for associations between disease outcomes and phenotypes.

Results At emergency department (ED) admission, the prevalence of pneumonia and hypoxaemia was 43% and 50%, respectively, and when stratified to phenotypes: 28.2% hypoxaemia$^+$/pneumonia$^+$, 22.2% hypoxaemia$^+$/pneumonia$^-$, 14.5% hypoxaemia$^-$/pneumonia$^+$ and 35.1% hypoxaemia$^-$/pneumonia$^-$. Mortality was 31.1% in the hypoxaemia$^+$/pneumonia$^-$ group and 26.3% in the hypoxaemia$^+$/pneumonia$^+$ group. Hypoxaemia with pneumonia and without pneumonia predicted higher probability of death. Hypoxaemia either <24 hours or ≥24 hours after hospitalisation predicted higher mortality and need for home oxygen compared with those without hypoxaemia. Patients with early hypoxaemia had higher probability of Intensive care unit (ICU) admission compared with those with late hypoxaemia.

Conclusion Mortality in COVID-19 infection is predicted by hypoxaemia with or without pneumonia and was greatest in patients who initially presented with hypoxaemia. The emergence of hypoxaemia was predicted by radiographic pneumonia. Patients with early and emergent hypoxaemia had similar mortality but were less likely to be admitted to ICU. There may be delayed identification of hypoxaemia, which prevents timely escalation of care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Real-world study looking at the outcomes of hospitalised COVID-19 patients based on the presence and/or absence of hypoxaemia and pneumonia.
⇒ Collection of extensive demographics and clinical features of patients with COVID-19 based on stratification into hypoxaemia and/or pneumonia.
⇒ Provide patient outcomes based on time course of hypoxaemia.
⇒ Arterial blood gases (ABG) and Partial pressure of oxygen (PaO2) to Fraction of inspired oxygen (FiO2) ratio was unfortunately unable to be assessed as not every patient had this data point collected.
⇒ Chest X-ray findings reported by one radiologist as opposed to two independent radiologists.

INTRODUCTION

The manifestations and clinical course of COVID-19 can be highly variable with numerous complications, including pneumonia, thromboembolic disease, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. Two important features, such as pneumonia and hypoxaemia, have been commonly described and contribute to high mortality and morbidity in COVID-19.[1 2] Hypoxaemia may arise from the ventilation/perfusion mismatch secondary to viral-induced lung infiltration and inflammation.[3] In itself, hypoxaemia may contribute to COVID-19 by promoting viral replication, lung inflammation, cytokine release, pulmonary vasoconstriction, and intravascular thrombosis.[3] The prevalence of hypoxaemia has been reported to range from 15% to 65% and is strongly associated with a worse outcome.[4–9] The other common manifestation of COVID-19 is pneumonia, which may

not be evident on the chest X-ray (CXR) at the time of presentation in up to 18% of mild COVID-19 cases and in 3% of patients with severe disease.[10] While these two clinical features have been commonly reported and described for the presentation of COVID-19, there is a paucity of data to inform the subsequent course of COVID-19 illness in patients presenting with and without hypoxaemia and pneumonia. A better understanding of their implication at the time of presentation can lead to earlier implementation of treatment strategies that can mitigate poor outcomes.

The aim of this study was to describe the prevalence and clinical course of hospitalised COVID-19 patients based on the initial presentation with and without oxygenation and pneumonia.

METHODS

Patient and public involvement

All data from the McMaster Multi-Regional Hospital Coronavirus Registry (COREG) were pseudonymised, and therefore, patients were not involved in the study.

Study design

This was a retrospective study using registry data collected on patients admitted with COVID-19 across six hospitals (three academic centres, three community hospitals) from the COREG. COREG was a multicentred database that deidentified secondary data (generated as part of clinical care) on hospitalised patients with positive PCR SARS-CoV-2 infection in Ontario, Canada.[11] Clinical data were only collected for 3 days after admission and again follow any change in clinical setting (eg, transfer to ICU), and at discharge. This study included patients admitted between March 2020 and June 2021 were included in the study.

Study population

All patients ≥18 years old with confirmed PCR+COVID-19 that were admitted between March 2020 and June 2021 were included. Patients with no lung imaging at presentation, and those admitted from a long-term care for solely for the purpose of isolation and without any medical sequala from COVID-19 infection, were excluded.

Patient phenotyping according to hypoxaemia and pneumonia

Patients were divided into four phenotypes based on the presence or absence of hypoxaemia and/or pneumonia at the time of presentation to the emergency department (ED): hypoxaemia$^+$/pneumonia$^+$, hypoxaemia$^+$/pneumonia$^-$, hypoxaemia$^-$/pneumonia$^+$, hypoxaemia$^-$/pneumonia$^-$. Hypoxaemia was defined as a resting pulse oximetry reading of <92% on room air and/or need for supplemental oxygen to maintain SpO2 ≥92%.[12] Both clinical and radiographic findings compatible with pneumonias was needed for the diagnosis of pneumonia, as previously described.[13 14]

Statistical analysis

Patients were stratified according to hypoxaemia/pneumonia phenotype and comparison of prevalence rates across cohorts was assessed by χ^2 analysis. Descriptive statistics were used to describe the cohorts and comparisons between groups were conducted using χ^2 for categorical variables and Analysis of Variance (ANOVA) tests for continuous variables. The primary outcome was a composite of mortality, ICU admission, and discharge on home oxygen across phenotypes and log-rank tests were used to test for differences. Comparison of survival distribution between cohort was performed using Kaplan-Meier (KM) curves and log-rank tests. Cox regression was used to calculate the adjusted HR for each phenotype controlling for age, sex and number of comorbidities. Where time-to-event data were not available, logistic regression was used to estimate the adjusted OR between disease outcomes and patient phenotypes, controlling for age, sex and comorbidities. Given the multiple comparisons, nominally significant p values should be interpreted cautiously, unless very small or the results form a coherent pattern. The statistical significance to a $p<0.05$. All analyses were done in SAS V.9.4.

RESULTS

Patient population

Of the 1612 patients screened for this study, 1466 PCR+COVID-19 patients met inclusion criteria (online supplemental figure 1). Of these, 739 patients (50.4%) had hypoxaemia and 626 patients (42.7%) had pneumonia at the time of presentation. Among these patients, a total of 414 (28.2%) were categorised as hypoxaemia$^+$/pneumonia$^+$, 325 (22.2%) as hypoxaemia$^+$/pneumonia$^-$, 212 (14.5%) as hypoxaemia$^-$/pneumonia$^+$ and 515 (35.1%) as hypoxaemia$^-$/pneumonia$^-$. The baseline characteristics for these groups are presented in online supplemental table 1.

Clinical, radiographic and laboratory findings at presentation

The median time from symptom onset to hospitalisation was 3 days (IQR 0–8), with significant differences observed between groups. In general, patients with pneumonia only (5 days, IQR 3–9) presented later, followed by those with hypoxaemia alone (5 days, IQR 2–9), and those without hypoxaemia or pneumonia presenting within 1 day of symptom onset. Commonly reported symptoms were dyspnoea (55.6%), cough (53.8%) and fatigue/malaise (39.2%) (online supplemental table 2), primarily in the hypoxaemia$^+$pneumonia$^+$ and hypoxaemia$^-$ pneumonia$^+$ groups. As expected, the groups with pneumonia had higher reported radiographic changes with consolidation being the most common finding, followed by opacification, interstitial changes and GGO. Further, those with hypoxaemia had higher rates of these findings that patients without hypoxaemia.

COVID-19 disease course, treatment and complications in hospitalised patients

The admitting rate to ICU from ED was 16.37% (n=240) and of those admitted to the ward (n=1145) a total of 141

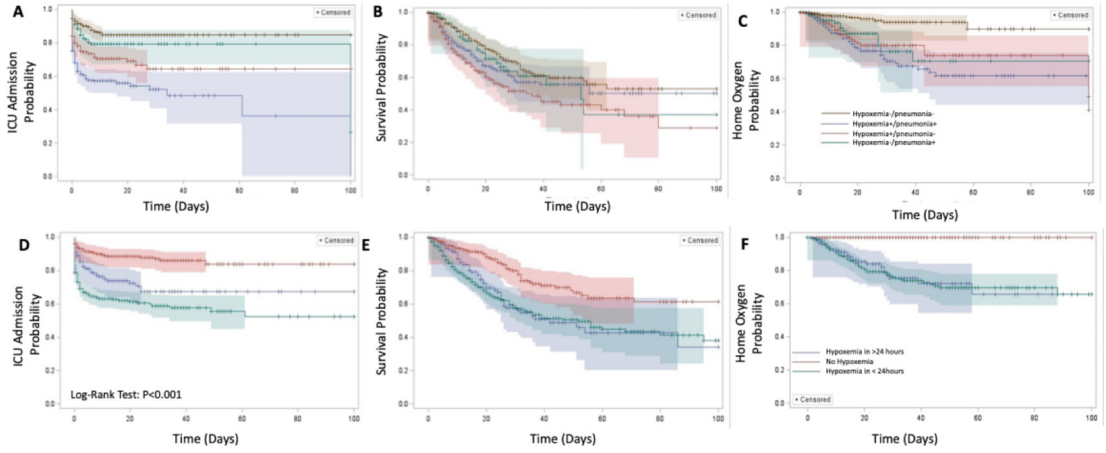

Figure 1 Kaplan-Meier survival analysis based on pneumonia and hypoxaemia. (A) Patients in the hypoxaemia$^+$/pneumonia$^+$ group were more likely to require ICU admission, whereas the hypoxaemia$^-$/pneumonia$^-$ group was least likely. In terms of mortality (B), patients in the hypoxaemia$^+$/pneumonia$^-$ group were least likely to survive compared with the hypoxaemia$^-$/pneumonia$^-$ group. At discharge, the group most likely to require home oxygen therapy (C) was the hypoxaemia$^+$/pneumonia$^+$ group compared with the hypoxaemia$^-$/pneumonia$^-$ group. (D) Patients with hypoxaemia in under 24 hours of hospital presentation were more likely to require Intensive Care Unit (ICU) admission sooner, whereas those who developed hypoxaemia after 24 hours of presentation were less likely to require ICU admission (p<0.001). (E) Regardless of the development of hypoxaemia in <24 or >24 hours, patients had a lower probability of survival compared with those without hypoxaemia during their hospital stay (p<0.001). (F) Similarly, patients who were hypoxaemic at any point during their hospital admission were more likely to require home oxygen compared with patients without hypoxaemia (p<0.001).

patients (9.6%) were later transferred to the ICU (online supplemental table 3). The hypoxaemia$^+$/pneumonia$^+$ group (n=120; 8%) was more likely to be admitted to ICU, and the least likely was the hypoxaemia$^-$/pneumonia$^-$ group (n=33; 2%). The hypoxaemia$^-$/pneumonia$^-$ group (n=454; 31%) was most likely to be admitted to the ward, while the hypoxaemia$^+$/pneumonia$^+$ (n=280; 3.8%) and hypoxaemia$^-$/pneumonia$^+$ (n=179; 1.4%) groups were most likely to be transferred from the ward to ICU. The median time to transfer from ward to ICU was 3 days (IQR 2–6), with the shortest time to transfer being the hypoxaemia$^+$/pneumonia$^+$ group (2 days, IQR 2–5) and longest time being the hypoxaemia$^-$/pneumonia$^-$ group (7.5 days, IQR 2–11). A total of 772 patients (53.3%) received corticosteroids, predominantly those within the hypoxaemia$^+$/pneumonia$^+$ and hypoxaemia$^+$/pneumonia$^-$ groups. The hypoxaemia$^+$/pneumonia$^+$ group was most likely to receive antibiotics, tocilizumab, high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV), proning and home oxygen at discharge (online supplemental table 3).

Mortality was 22.9% among all hospitalised patients, being highest in the hypoxaemia$^+$/pneumonia$^-$ group (n=101, 31%) and lowest in the hypoxaemia$^-$/pneumonia$^+$ group (n=33, 15.6%). The KM curve showed that the probability of mortality was highest in the hypoxaemia$^+$/pneumonia$^-$ and hypoxaemia$^-$/pneumonia$^+$ groups (figure 1). The median shortest time to death was in the hypoxaemia$^+$/pneumonia$^+$ (12 days) and hypoxaemia$^+$/pneumonia$^-$ (11 days) groups. Controlling for age, sex and comorbidities, the HR for complications between groups are provided in figure 2. The presence of hypoxaemia with and without pneumonia and without pneumonia were similar in predicting the highest probability of death. Similarly, hypoxaemia was a significant predictor for ICU admission and of the need for HFNC, IMV and NIV. Female sex was associated with a lower risk of death, HFNC and IMV use. The presence of two or more comorbidities was a positive predictor for death. Lastly, hypoxaemia with pneumonia was a positive predictor for home oxygen prescription at discharge.

The most common complications were acute renal failure, pleural effusion and ARDS (online supplemental table 3). Pulmonary embolism (PE) accounted for 4.6% of all complications. Those with hypoxaemia were more likely to have a PE (OR 2.73) or deep vein thrombosis (OR 4.2).

Development of hypoxaemia and pneumonia during hospitalisation and related complications

Among the 968 patients with hypoxaemia during hospitalisation, 76.3% (n=739) presented with early hypoxaemia (within 24 hours), and 23.7% (n=229) developed emergent hypoxaemia after >24 hours of admission. The presence of pneumonia at admission was significantly associated with an adjusted OR of 2.10 for the development of hypoxaemia following admission (online supplemental table 4).

Of the 739 patients with early hypoxaemia, 270 (34%) were admitted to ICU during hospitalisation, with 190 (26%) patients admitted directly from ED and 80 (45%) patients later transferred from the ward. The median time from ward to ICU transfer was 3.0 days (IQR 2–5) vs 4 days (IQR 4–8) with the emergent hypoxaemia group. In contrast, of the 229 emergent hypoxaemia patients, 58

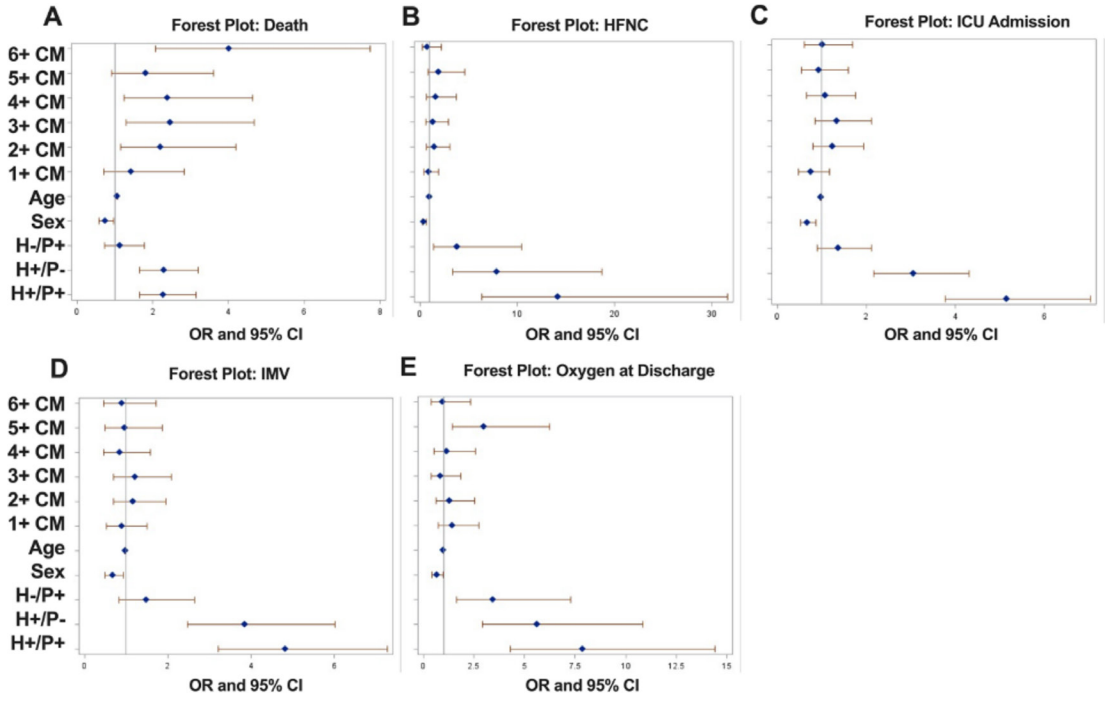

Figure 2 OR of adverse outcomes in COVID-19 patients logistic regression was used to develop forest plots showing the OR and 95% CI for various adverse outcomes including death (A), use of high-flow nasal cannula (HFNC) (B), Intensive Care Unit (ICU) admission (C), use of invasive mechanical ventilation (IMV) (D), and requirement of home oxygen at discharge (E). The OR for these outcomes was adjusted for number of comorbidities (CM), age, sex, hypoxaemia (H) and/or pneumonia (P).

(25%) were admitted to the ICU during hospitalisation, with 21 (36%) being directly from ED and 37 (64%) later transferred from the ward). As per the KM curve, patients with early hypoxaemia had higher probability of ICU admission than emergent hypoxaemia (figure 1). Further, the early hypoxaemic group compared with the emergent group had a longer mean length of stay (LOS) in ICU (9 vs 7 days) and higher rates of IMV use (21% vs 11%) (online supplemental table 5). There were similar rates of systemic corticosteroid use in the early versus emergent hypoxaemic group (66.9% vs 65%) and death (28.4% vs of those with early hypoxaemia died 27.5%; p<0.05).

With respect to pneumonia, 626 (43%) patients had a clinical-radiographic pneumonia syndrome at some point during hospitalisation, of which 378 (60%) had pneumonia at presentation. Of the 592 patients without pneumonia at presentation, 248 (41.9%) went on to develop pneumonia during hospitalisation. The development of pneumonia was more common in the hypoxaemia$^+$/pneumonia$^-$ group (40%) than the hypoxia$^-$/pneumonia$^-$ group (22.5%).

DISCUSSION

In a cohort of 1466 hospitalised patients with COVID-19, we retrospectively compared the prevalence and time course of patients presenting with pneumonia or hypoxaemia alone and in combination. Approximately 40% of patients had clinical and radiographic findings suggestive of pneumonia. This proportion is comparable to a previous study involving a Thailand patient cohort.[15] The prevalence of hypoxaemia was 50%, falling within the range of 15%–65% documented in recent literature.[4–7] When stratified into phenotypes, 35.1% of patients had hypoxaemia$^-$/pneumonia$^-$, 28.2% had hypoxaemia$^+$/pneumonia$^+$, 22.2% had hypoxaemia$^+$/pneumonia$^-$ and 14.5% had hypoxaemia$^-$/pneumonia$^+$. Most importantly, the presence of hypoxaemia alone or in combination with pneumonia predicted worse clinical outcomes, including mortality.

Although the hypoxaemia$^-$/pneumonia$^-$ and hypoxaemia$^+$/pneumonia$^+$ groups were most prevalent, patients with either hypoxaemia or pneumonia alone still made up a substantial proportion. The overall mortality was 22.9%, consistent with previous reports ranging from 11.5% to 32%.[16–19] These mortality rates underscore the need to identify patients at high risk for decompensation to allow for proper escalation of care. When examined according to phenotype, the hypoxaemia$^+$/pneumonia$^+$ group had a mortality of 26.3%. Interestingly, patients with hypoxaemia alone had a higher mortality (31%) and HR for predicting mortality. In line with this, a shorter LOS in hospital was seen with patients that had hypoxaemia and/or pneumonia, which may have been due to higher mortality rate. This raises the question of why the hypoxaemia$^+$/pneumonia$^-$ group had poorer mortality outcomes. A total of 36% of hypoxaemia$^+$/pneumonia$^-$ patients developed pneumonia later during their hospitalisation, which could have contributed to mortality. The window between admission and decompensation (ie, ward to ICU transfer) appeared to be similar between

the hypoxaemia$^+$/pneumonia$^-$ group and hypoxaemia$^+$/pneumonia$^+$ group at 2–3 days. Although the groups had a similar time frame of decompensation, the hypoxaemia$^+$/pneumonia$^-$ group overall was 50% less likely to be admitted to ICU than the hypoxaemia$^+$/pneumonia$^+$ group, despite similarities in oxygen requirements, ICU and hospital LOS, and overall complications. The hypoxaemia$^+$/pneumonia$^-$ group was also less likely to receive pharmacological management or ventilatory support. Despite all hypoxaemia$^+$/pneumonia$^-$ patients meeting criteria for corticosteroids,[20] 10% fewer patients received dexamethasone compared with the hypoxaemia$^+$/pneumonia$^+$ group (however, there was little difference in corticosteroid administration between early and emergent hypoxaemia). The hypoxaemia$^+$/pneumonia$^-$ group was also 50% less likely to undergo proning compared with the hypoxaemia$^+$/pneumonia$^+$ group. On discharge, 5% more of the hypoxaemia$^+$/pneumonia$^+$ patients were prescribed home oxygen compared with those with hypoxaemia alone. Prompt escalation of care may not have occurred due to the occult presentation of hypoxaemia$^+$/pneumonia$^-$ patients. Unfortunately, they had a similar propensity for decompensation compared with hypoxaemia$^+$/pneumonia$^+$ patients, further highlighting disease that is difficult to predict, particularly when applying common clinical heuristics. There appears to be a missed opportunity for management that could potentially change disease outcomes in those presenting exclusively with hypoxaemia.

To further understand disparities in care between the hypoxaemia$^+$/pneumonia$^+$ and hypoxaemia$^+$/pneumonia$^-$ groups, we stratified patients based on hypoxaemia timeline. To our knowledge, this is the first large retrospective study (through multiple pandemic waves) that has looked at the development of hypoxaemia <24 (early) vs ≥24 (emergent) hours. Patients with early hypoxaemia were more likely to require ICU admission compared with those with emergent hypoxaemia. The early group was also more likely to be admitted directly from ED to ICU. Conversely, more than 80% of the emergent hypoxaemia group was later transferred from ward to ICU during their hospitalisation, within a median of 4 days. The early group was more likely to receive pharmacological and ventilatory management. Overall, these groups had similar outcomes with respect to mortality (27.5% vs 28.4%), but time to death was shorter in the early group (11 vs 17 days). In addition, the likelihood of home oxygen at discharge was similar between those groups (13% vs 12.5%). These findings are similar to Suh *et al* who compared hypoxaemia <3 days vs ≥3 days of hospital presentation and found similar inpatient mortality and that these patients were more likely to require IMV.[7] They also found several predictive variables of early oxygen requirements including age, delay in hospital admission and CXR abnormalities.[7] Further, the aforementioned findings demonstrate that hypoxaemia, regardless of the presence of pneumonia or hypoxaemia timeline, resulted in a complicated disease course. This may be attributable to the lack of hypoxaemia at initial presentation providing false reassurance, and the difficulty of predicting emergent hypoxaemia during hospitalisation. As per our regression model, the presence of pneumonia, but no other notable baseline characteristics, predicted emergent hypoxaemia. Overall, the absence of hypoxaemia at ED presentation does not appear to be reassuring for good outcomes, which is crucial to consider during ED triage. Patients who seem well, with no evidence of hypoxaemia or pneumonia, may benefit from virtual monitoring with a lower threshold for escalation of care, due to the difficulty of identifying at-risk patients for emergent hypoxaemia. What is less clear is how to approach the pneumonia-only group. Although they had similar mortality to the hypoxaemia$^-$/pneumonia$^-$ group, ICU and oxygen requirements were comparable to the hypoxaemia$^+$/pneumonia$^-$ and hypoxaemia$^+$/pneumonia$^+$ groups. This could be due to approximately 50% developing late hypoxaemia. Close monitoring should also be considered in this group given this relatively high risk of decompensation. Given that recent work has associated the duration of hypoxaemia with poor outcomes,[21] it would have been interesting to examine this in our study, but daily data were not available in COREG.

What was probably the most surprisingly and unexpected finding in this study was the poor outcomes for the hypoxaemia$^-$/pneumonia$^-$ group with an overall mortality of 18.1%. Similarly, Adams *et al* reported a 32% mortality in COVID-19 patients without hypoxia.[22] Among these patients, 14% still required ICU admission, and had a longer window of decompensation with ward to ICU transfer of 7.5 days. It appears that the initial stability of these patients is not reassuring and is a patient subgroup that requires careful monitoring. This begs the question as to whether there were other non-COVID contributing factors to this patient group, but these patients had similar age and comorbidities compared with the other phenotype groups. Further research is needed to determine additional non-respiratory mechanisms that may contribute to mortality in patients without hypoxaemia or pneumonia.

This study had some limitations. All data extracted came from secondary sources, and as such certain variables were not collected in a majority of the cohort. As ABGs were not performed in most patients, we used oximeter readings rather than ABGs to assess oxygen status. A notable limitation to the pulse oximetry is the potential inaccurate readings in patients with darker skin colour.[23] In addition, CXR images were read by a single clinical radiologist. While it may have been ideal to have CXR findings reported by two independent radiologists, these were not available within the confines of COREG. There is some merit in that the study design reflects real-world practice, where oximeters are primarily relied on for non-ICU management, and only one clinical radiologist provides reports. Further, this study was retrospective in nature, which may have led to certain biases in data

registration and collection. Our hospital management guidelines may differ from other regions, which can be seen in reference to the low corticosteroid use in our cohort. It is unclear why a low proportion of patients received dexamethasone despite meeting inclusion criteria as per the RECOVERY trial.[24] However, it may be due to lack of robust evidence for dexamethasone in the first COVID-19 wave.

A distinct strength of this study was a cohort consisting of almost 2000 patients from 6 hospitals in Southern Ontario with a catchment of 1 000 000 people, including both academic and community hospitals. This large number of patients combined with a less stringent inclusion criteria and multicentre cohort increases the generalisability of the study. Our depth of data collection is also a strength, especially given the recorded time courses during hospitalisation. In addition, given this was a study in Canadian healthcare, the public taxpayer system minimised selection bias due to universal healthcare access.

This study assessed not only the prevalence of hypoxaemia and pneumonia in the form of four unique phenotypes and compare disease outcomes, but also the first study in North America to look at differences in early versus emergent hypoxaemia. While hypoxaemia and pneumonia are common features on presentation to hospital, patients without these features are still at risk of decompensation. Unfortunately, the lack of hypoxaemia or pneumonia is not entirely reassuring, and even patients without these features have a high rate of mortality, and as such, this patient group may require close monitoring. In addition, particular attention should be paid to patients with exclusively hypoxaemia, regardless of associated dyspnoea, as the disease course is less predictable. A lower threshold should be implemented to monitor these patients and escalate care. Emergent hypoxaemia is common, predicted only by radiographic pneumonia, and appears to be under-recognised, which may contribute to delayed escalation of care and subsequently higher mortality.

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Contributors BS and BD conducted the data collection, analysis and wrote the paper. LS, JK, CL and TP assisted with data collection. SQ, LD, MJ, AJ, MB, RK, MD, APC, JLYT assisted with study design, data analysis and writing of the paper. TH was involved in the study design, data collection analysis and writing of the paper. TH is the corresponding author and principal investigator for this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the local research ethics board from the Hamilton Research Ethics Board (#10841) and Tri-Hospital Research Ethics Board (#2020-0699). Informed consent was waivered as this was a retrospective chart review.

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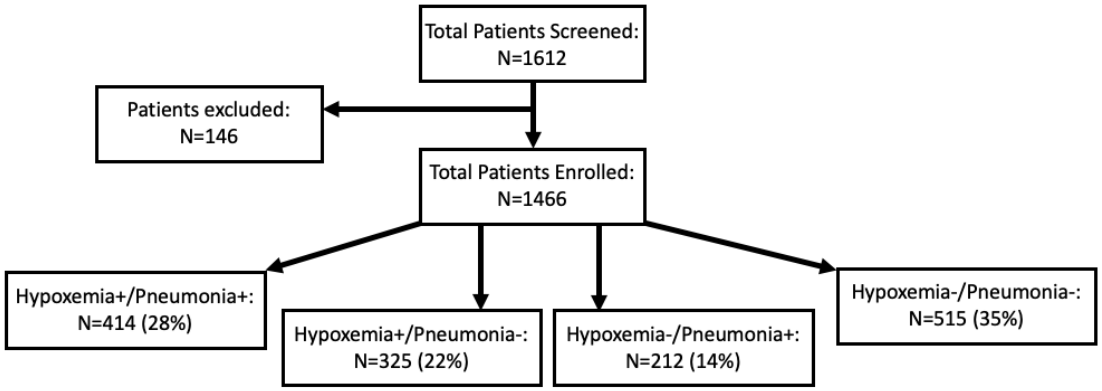
ONLINE SUPPLEMENTARY FIGURES & TABLES



Supplementary Figure 1: Consort Diagram

A total of 1,612 patients were screened for study enrollment, with 146 patients being excluded due to no chest x-ray (CXR) imaging being conducted within the emergency department (ED) or on day 1 of admission or being admitted from long term care (LTC) due isolation as opposed to medical issues. Out of the 1603 patients enrolled in this retrospective study, 414 (25.8%) were in the hypoxemia^{+}/pneumonia^{+} group, 325 (20.3%) in the hypoxemia^{+}/pneumonia^{-} group, 212 (13.2%) in the hypoxemia^{-}/pneumonia^{+} group, and 515 (35.1%) in the hypoxemia^{-}/pneumonia^{-} group.

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	All Patients (N=1466)	Hypoxemia⁻ Pneumonia⁻ (N=515)	Hypoxemia⁻ Pneumonia⁺ (N=212)	Hypoxemia⁺ Pneumonia⁻ (N=325)	Hypoxemia⁺ Pneumonia⁺ (N=414)	P Values
Age (Mean, SD)	70.4 (17.1)	70.6 (19.1)	66.9 (18.4)	73.7 (14.3)	69.3 (15.5)	**<0.001***
Sex (Male)	798 (54.4%)	268 (52.0%)	126 (59.4%)	180 (55.4%)	224 (54.1%)	0.33
Rural Hospital Site	788 (53.7%)	257 (49.9%)	111 (52.4%)	193 (59.4%)	227 (54.8%)	**0.006***
City Hospital Site	678 (46.3%)	258 (50.1%)	101 (47.6%)	132 (40.6%)	187 (45.2%)	
Comorbidities:						
Hypertension, no. (%)	874 (59.6%)	304 (59.0%)	109 (51.4%)	200 (61.5%)	261 (63.0%)	**0.04***
Coronary Artery Disease, no. (%)	296 (20.2%)	99 (19.2%)	43 (20.3%)	72 (22.2%)	82 (19.8%)	0.91
Heart Disease, no. (%)	225 (15.4%)	81 (15.7%)	28 (13.2%)	52 (16.0%)	64 (15.5%)	0.94
Diabetes (no insulin), no. (%)	331 (22.6%)	112 (21.8%)	47 (22.2%)	71 (21.9%)	101 (24.4%)	0.91
Diabetes (insulin), no. (%)	175 (11.9%)	66 (12.8%)	28 (13.2%)	41 (12.6%)	40 (9.7%)	0.69
Atrial Fibrillation, no. (%)	282 (19.2%)	106 (20.6%)	42 (19.8%)	67 (20.6%)	67 (16.2%)	0.59
Chronic Kidney Disease no. (%)	208 (14.2%)	84 (16.3%)	29 (13.7%)	41 (12.6%)	54 (13.0%)	0.67
Obesity, no. (%)	155 (10.6%)	45 (8.7%)	18 (8.5%)	39 (12.0%)	53 (12.8%)	0.12
Ischemic Stroke, no. (%)	166 (11.3%)	70 (13.6%)	21 (9.9%)	40 (12.3%)	35 (8.5%)	0.19
Asthma, no. (%)	134 (9.1%)	39 (7.6%)	20 (9.4%)	28 (8.6%)	47 (11.4%)	0.50
ED Symptoms:						
Days since sx onset, median (IQR)	3.0 (0.0-8.0)	1.0 (0.0-6.0)	5.0 (3.0-9.0)	3.0 (0.0-8.0)	5.0 (2.0-9.0)	**<0.001***
Cough, no. (%)	786 (53.8%)	177 (34.6%)	155 (73.1%)	152 (47.1%)	302 (73.0%)	**<0.001***
Productive Cough, no. (%)	226 (15.5%)	45 (8.8%)	56 (26.4%)	23 (7.1%)	102 (24.6%)	**<0.001***
Dyspnea, no. (%)	812 (55.6%)	123 (24.1%)	152 (71.7%)	180 (55.7%)	357 (86.2%)	**<0.001***
Fever, no. (%)	377 (25.7%)	78 (15.2%)	71 (33.5%)	73 (22.5%)	155 (37.4%)	**<0.001***
Fatigue/Malaise, no. (%)	572 (39.2%)	157 (30.7%)	106 (50.0%)	115 (35.6%)	194 (46.9%)	**<0.001***
Myalgia, no. (%)	150 (10.3%)	38 (7.4%)	35 (16.5%)	29 (9.0%)	48 (11.6%)	**<0.002***
Headache, no. (%)	114 (7.8%)	30 (5.9%)	28 (13.2%)	16 (5.0%)	40 (9.7%)	**<0.001***
Diarrhea, no. (%)	272 (18.6%)	70 (13.7%)	69 (32.6%)	46 (14.2%)	87 (21.0%)	**<0.001***
Vomiting/Nausea, no. (%)	250 (17.1%)	69 (13.5%)	49 (23.1%)	50 (15.5%)	82 (19.8%)	**0.005***
Altered LOC, no. (%)	304 (20.8%)	109 (21.3%)	33 (15.6%)	88 (27.1%)	74 (17.9%)	**0.014***
Sore throat, no. (%)	89 (6.1%)	23 (4.5%)	21 (9.9%)	11 (3.4%)	34 (8.2%)	**<0.002***
Rhinorrhea, no. (%)	65 (4.5%)	18 (3.5%)	13 (6.1%)	14 (4.3%)	20 (4.8%)	0.46
Chest Pain, no. (%)	154 (10.6%)	36 (7.1%)	39 (18.4%)	29 (9.0%)	50 (12.1%)	**<0.001***

Supplementary Table 1: Demographics and characteristics in patients with COVID-19

CLD: Chronic lung disease, LOC: Level of Consciousness, No: Number, SD: Standard Deviation, Sx: Symptom.

This table demonstrates the patient demographics and characteristics across the four different phenotypes (with or without hypoxemia and pneumonia). Between group comparisons were conducted with a one-way ANOVA. Statistical significance was set to P<0.05. All values are the number of patients with percentage, unless otherwise stated.

Laboratory Investigations in patients with COVID-19 at initial hospital presentation							
Total Patients N= 1466	**Reference Values**	**All Patients (N= 1466)**	**Hypoxemia⁻ Pneumonia⁻ (N=515)**	**Hypoxemia⁻ Pneumonia⁺ (N=212)**	**Hypoxemia⁺ Pneumonia⁻ (N=325)**	**Hypoxemia⁺ Pneumonia⁺ (N=414)**	**P Values**
ED Bloodwork:							
WBC x10^9/mL, median (IQR)	4-11	7.2 (5.3 – 10.2)	7.2 (5.2 – 10.8)	6.2 (4.7 – 8.3)	7.6 (5.7 – 11.1)	7.6 (5.5 – 10.3)	**<0.001***
Neut x10^9/mL, median (IQR)	2-7	5.5 (3.7 – 8.1)	5.2 (3.4 – 8.3)	4.8 (3.3 – 6.4)	6.0 (4.0 – 8.8)	5.9 (4.0 – 8.4)	**<0.001***
Eos x10^9/mL, median (IQR)	0-0	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.0)	**<0.001***
Lymph x10^9/mL, median (IQR)	1-4	0.9 (0.6 – 1.3)	1.0 (0.7 – 1.5)	0.8 (0.6 – 1.1)	0.9 (0.6 – 1.2)	0.8 (0.5 – 1.2)	**<0.001***
Platelets x10^9/mL, median (IQR)	150-400	208.0 (160.0 – 269.0)	218.0 (161.0 – 281.0)	186.0 (149.0 – 246.0)	212.0 (158.0 – 272.0)	202.0 (162.0 – 265.0)	**0.018***
Ferritin µg/L, median (IQR)	<100	560.0 (247.0 – 1039.0)	195.0 (125.0 – 375.0)	551.0 (283.0 – 897.6)	463.1 (195.5 –	830.0 (433.0 –	**<0.001***
D-dimer mg/L, median (IQR)	<500	1.3 (0.7-3.0)	1.2 (0.6 – 2.2)	0.8 (0.5 – 1.6)	1054.5)	1390.0)	**0.003***
CRP mg/L, median (IQR)	<10	79.5 (35.2 – 153.5)	41.7 (13.2 – 104.7)	50.4 (19.1 – 99.0)	1.3 (0.6 – 3.7)	1.4 (0.8 – 3.6)	**<0.001***
					99.9 (44.3 – 156.3)	122.0 (66.6 – 181.5)	
CXR Features:							
Opacity, no. (%)	-	286 (19.5%)	14 (2.7%)	106 (50.0%)	12 (3.7%)	154 (37.2%)	**<0.001***
Consolidation, no. (%)	-	378 (25.8%)	9 (1.8%)	99 (46.7%)	20 (6.2%)	250 (60.4%)	**<0.001***
GGO, no. (%)	-	77 (5.3%)	2 (0.4%)	27 (12.7%)	3 (0.9%)	45 (10.9%)	**<0.001***
Interstitial, no. (%)	-	189 (12.9%)	7 (1.4%)	46 (21.7%)	6 (1.9%)	130 (31.4%)	**<0.001***
Effusion, no. (%)	-	155 (10.6%)	24 (4.7%)	19 (9.0%)	27 (8.3%)	85 (20.5%)	**<0.001***

Supplementary Table 2: Investigations at initial presentation to ED for all patients with COVID-19 infection

This table demonstrates the laboratory and radiographical findings between all four patient phenotypes based on expression of hypoxemia and pneumonia. Between group comparisons were conducted with a one-way ANOVA. Statistical significance was set to P<0.05. All data are presented as median with interquartile range (IQR) or mean with percent.

CRP: C-reactive protein, CXR: Chest x-ray, Eos: Eosinophils, GGO: Ground glass opacities, IQR: Interquartile range, Lymph: Lymphocytes, Neut: Neutrophils, WBC: White blood cell

Disease Course & Treatment in Hospital						
Total Patients N= 1466	**All Patients (N=1466)**	**Hypoxemia⁻ Pneumonia⁻ (N=515)**	**Hypoxemia⁻ Pneumonia⁺ (N=212)**	**Hypoxemia⁺ Pneumonia⁻ (N=325)**	**Hypoxemia⁺ Pneumonia⁺ (N=414)**	**P Values**
Respiratory Therapy:						
HFNC, no. (%)	96 (6.6%)	7 (1.4%)	9 (4.3%)	25 (7.7%)	55 (13.3%)	**<0.001***
NIV, no. (%)	23 (1.6%)	1 (0.2%)	0 (0.0%)	8 (2.5%)	14 (13.4%)	**<0.001***
Daily NIV, no. (%)	120 (8.3%)	21 (4.1%)	9 (4.3%)	35 (10.9%)	55 (13.4%)	**<0.001***
IMV, no (%)	211 (14.4%)	36 (7.0%)	20 (9.4%)	59 (18.2%)	96 (23.2%)	**<0.001***
Home Oxygen Therapy, no (%)	122 (8.3%)	14 (2.7%)	16 (7.55%)	32 (9.85%)	60 (14.5%)	**<0.001***
Prone Ventilation, no (%)	121 (8.3%)	10 (2.0%)	19 (9.0%)	26 (8.2%)	66 (16.1%)	**< 0.001***
Pharmacological Therapy:						
Corticosteroids, no. (%)	772 (53.3%)	171 (33.6%)	113 (53.6%)	194 (61.0%)	294 (71.5%)	**<0.001***
Tocilizumab, no. (%)	61 (4.2%)	6 (1.2%)	13 (6.2%)	13 (4.1%)	29 (7.1%)	**<0.001***
Antibiotics, no. (%)	1070 (73.8%)	308 (60.5%)	166 (78.7%)	233 (73.3%)	363 (88.3%)	**<0.001***
ICU Admission	381 (26.0%)	79 (14.0%)	38 (18.0%)	96 (30%)	175 (42.0%)	**<0.001***
Time to ICU transfer, median (IQR)	3.0 (2.0 – 6.0)	7.5 (2.0 – 11.0)	3.0 (2.0 – 4.0)	3.0 (2.0 – 8.0)	2.0 (2.0 –5.0)	**0.004***
ICU Duration, median (IQR)	8.0 (4.0 – 16.0)	5.0 (3.0 – 11.0)	8.0 (5.0 – 13.0)	9.0 (3.0 – 18.0)	8.5 (4.0 – 17.0)	**0.011***
LOS Hospital, median (IQR)	11.0 (5.0 – 22.0)	12.0 (5.0 – 30.0)	8.0 (4.0 – 16.0)	10.0 (5.0 – 21.0)	10.0 (5.0 – 20.0)	**<0.007***
Time to Death, median (IQR)	14.0 (8.0-24.0)	16.0 (9.0 – 31.0)	17.0 (13.0 – 26.0)	11.0 (7.0 – 21.0)	12.0 (7.0 – 23.0)	**0.03***
Mortality, no. (%)	336 (22.9%)	93 (18.1%)	33 (15.6%)	101 (31.1%)	109 (26.3%)	**<0.001***
Complications:						
Atrial Fibrillation, no. (%)	132 (9.1%)	40 (7.9%)	21 (10.0%)	28 (8.8%)	43 (10.5%)	0.35
ARDS, no. (%)	151 (10.4%)	20 (4.0%)	22 (10.4%)	32 (10.0%)	77 (18.7%)	**<0.001***
Bacteremia, no. (%)	105 (7.3%)	44 (8.6%)	9 (4.3%)	27 (8.5%)	25 (6.1%)	0.21
Congestive Heart Failure, no. (%)	115 (7.9%)	30 (5.9%)	19 (9.0%)	28 (8.8%)	38 (9.3%)	0.33
Cardiac Ischemia, no. (%)	119 (8.2%)	41 (8.1%)	14 (6.6%)	31 (9.8%)	33 (8.0%)	0.62
Deep Vein Thrombosis, no. (%)	41 (2.8%)	5 (1.0%)	3 (1.4%)	20 (6.3%)	13 (3.2%)	**<0.001***
Pulmonary Embolism, no. (%)	66 (4.6%)	14 (2.8%)	4 (1.9%)	21 (6.6%)	27 (6.6%)	**<0.003***
Pleural Effusion, no. (%)	186 (12.8%)	57 (11.2%)	12 (5.7%)	53 (16.7%)	64 (15.6%)	**<0.001***
Renal Failure (Acute), no. (%)	311 (21.5%)	98 (19.3%)	44 (20.9%)	68 (21.4%)	101 (24.6%)	0.41

Supplementary Table 3: COVID-19 Disease Course, Treatment, Complications and Outcomes

HFNC: High flow nasal cannula, NIV: Non-invasive ventilation, IMV: Invasive mechanical ventilation, LOS: Length of stay, ARDS: Acute Respiratory Distress Syndrome, no=number, IQR=Interquartile range.

This table demonstrates the differences in variables related to disease course, treatment, complications, and outcomes between all four patient phenotypes based on expression of hypoxemia and pneumonia. Between group comparisons were conducted with a one-way ANOVA. Statistical significance was set to P<0.05. All values are the number of patients with percentage, unless otherwise stated.

Effect	Point Estimate	95% Wald Confidence Limits	
Age	1.007	0.994	1.019
Sex (Female vs Male)	0.952	0.651	1.393
Comorbidities 1 vs 0	0.732	0.373	1.434
Comorbidities 2 vs 0	0.903	0.448	1.821
Comorbidities 3 vs 0	0.784	0.370	1.664
Comorbidities 4 vs 0	1.393	0.663	2.929
Comorbidities 5 vs 0	0.62	0.272	1.411
Comorbidities 6+ vs 0	1.357	0.631	2.919
Respiratory Rate	1.016	0.974	1.06
Oxygen Saturation (SpO2)	0.733	0.66	0.815
Pneumonia (Yes or No)	2.055	1.378	3.063
Days Since Symptom Onset	1.005	0.998	1.02

Supplementary Table 4: Predictive Model for Developing Hypoxemia more than 24 hours after Hospital Admission.

Outcomes based on hypoxemia time-course			
Total Patients N= 968	**Hypoxemic <24 hours (N=739)**	**Hypoxemia ≥24 hours (N=229)**	**P Values**
Home Oxygen Therapy, no. (%)	92 (12.5%)	30 (13.1%)	0.80
Non-Invasive Ventilation, no. (%)	90 (12%)	22 (9.6%)	0.50
High-Flow Nasal Canula, no. (%)	80 (10.8%)	8 (3.5%)	**<0.001***
Invasive Ventilation, no. (%)	155 (21.0%)	25 (10.9%)	**<0.001***
ICU Admission, no. (%)	270 (36.5%)	58 (25.3%)	**0.002***
Mortality, no. (%)	210 (28.4%)	63 (27.5%)	0.79
Time to Death (days), median (IQR)	11 (7-23)	17 (10-27)	**0.01***
Time to ICU transfer, median (IQR)	3.0 (2-5)	4 (2-8)	**0.048***
LOS in ICU (days), median (IQR)	9 (4-17)	7 (4-13)	0.09
LOS in ICU (days), mean (SD)	14.22 (15)	8.9 (6.7)	**<0.001***
LOS in Hospital (days), median (IQR)	10 (5-21)	12 (7-26)	**0.003***

Supplementary Table 5: Outcomes Based on Hypoxemia Time-Course during COVID Infection

LOS: Length of stay, IQR: Interquartile range, no: Number.

This table demonstrates the differences in outcomes between patients with early (<24 hours) or emergent (≥ 24 hours) hypoxemia. Comparisons were done with a chi-square for categorical values or unpaired t-test for nominal values. Statistical significance was set to P<0.05. All values are the number of patients with percentage, unless otherwise stated.