Silent hypoxia is not an identifiable characteristic in patients with COVID-19 infection

(Short title: Silent hypoxia is not unique to COVID-19 infection)

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Abstract

Background We aimed to assess whether asymptomatic ("happy") hypoxia was an identifiable physiological phenotype of COVID-19 acute respiratory distress syndrome (ARDS), and associated with need for ICU admission.

Methods We performed an observational cohort study of all adult patients admitted with hypoxaemic respiratory failure to a large acute hospital Trust serving the East Midlands, UK. Patients with confirmed COVID-19 were compared to those without. Physiological response to hypoxaemia was modelled using a linear mixed effects model.

Results Of 1,586 patients included, 75% tested positive for SARS-CoV-2. The ROX index was 2.08 min^{-1} lower (1.56 – 2.61, $p<0.001$) in the COVID-19 cohort when adjusted for age and ethnicity, suggesting an enhanced respiratory response to hypoxia compared to the non-Covid-19 patients. There was substantial residual inter- and intra-patient variability in the respiratory response to hypoxaemia. 33% of the infected cohort required ICU, and of these 31% died within 60 days. ICU admission and mortality were both associated with an enhanced respiratory response for all degrees of hypoxaemia.

Conclusions Patients with COVID-19 display a more symptomatic phenotype in response to hypoxaemia than those with other causes of hypoxaemic respiratory failure, however individual patients exhibit a wide range of responses. As such although asymptomatic hypoxaemia may be a phenomenon in any individual patient with hypoxaemic respiratory failure, it is no more frequently observed in those with SARS-CoV-2 infection than without.

Key words
Hypoxaemia, ARDS, COVID-19, clinical deterioration

Abbreviations

- ARDS: Acute respiratory distress syndrome
- AUC: Area under the curve
- COVID-19: Coronavirus disease, caused by SARS-CoV-2
- FiO_2: Fraction of inspired oxygen
- ICU: Intensive care unit
- PaO_2: Arterial oxygen tension
- PFR: PaO_2/FiO_2 ratio
- ROC curve: Receiver operating characteristic curve
- ROX index : Respiratory rate-oxygenation index
- SaO_2: Arterial oxygen saturation
- SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
- SpO_2: Oxygen saturation potential
- SFR: SpO_2/FiO_2 ratio

Introduction

The syndrome of “silent hypoxaemia” – hypoxaemia that is well tolerated with relatively less dyspnoea than the treating clinician expects – and the corresponding colloquialism “happy hypoxia” have been introduced into both clinical and journalistic settings to describe individual patients’ physiological response to COVID-19 pneumonitis[1] . However, it is unclear if asymptomatic hypoxaemia is a real phenomenon[2], or simply a label given to individual patients who are memorable outliers in terms of their expected respiratory response to hypoxaemia[3], regardless of their SARS-CoV-2 infection status[4].

Although asymptomatic hypoxaemia initially described patients with COVID-19 who presented with the absence of dyspnoea in the context of severe hypoxemia[5], the objective measurement of respiratory drive (tidal volume or mean inspiratory flow) or subjective assessment of work of breathing is often poorly documented in clinical practice for patients outside of ICU[6]. As such the physiological response to hypoxaemia, as recorded by nursing staff as routine observations[7], is increasingly being considered a proxy for “happiness” or otherwise in response to hypoxaemia in the context of SARS-CoV-2 infection[8] as a marker for a lack of abnormality in overall breathing pattern[9].

Initial recommendations were to be wary of treating hypoxaemia without signs of respiratory distress[10], however subsequent analyses considered asymptomatic hypoxaemia a risk factor for poor outcomes[5]. Hypoxaemia relative to fraction of inspired oxygen (FiO_2) is thought to be a better marker of severity of COVID-19 than absolute hypoxaemia[11], a relationship quantified using the SpO_2/FiO_2 Ratio (SFR) [12,13]. The SFR is used analogously to the PaO_2/FiO_2 ratio, which defines severity of Acute Respiratory Distress Syndrome (ARDS) in ventilated patients[14], with lower values reflecting a worsening degree of hypoxaemia relative to inspired oxygen. The respiratory rate-oxygenation (ROX) index[15,16], or ratio of SFR to respiratory rate, derived to quantify the risk of failure of high-flow oxygenation in all-comers with respiratory failure, may be predictive of need for intubation in COVID-19 patients[17–20]. The association between a higher respiratory rate for a given degree of relative hypoxaemia (and hence a lower ROX score) and failure of non-invasive oxygenation contradicts the concern that asymptomatic hypoxaemia may be associated with adverse outcomes.

As such, we aimed to assess if a distinct physiological phenotype of “happy hypoxia” in patients with COVID-19 was an identifiable clinical entity by considering the differences in the physiological response to both absolute hypoxaemia (measured by peripheral oxygen saturation, SpO_2, regardless of inspired oxygen) and relative hypoxaemia (by calculating the SFR) between patients admitted with COVID-19, and those who had hypoxaemia respiratory failure from causes other than

COVID-19. We also aimed to assess whether those patients suffering from COVID-19 who deteriorated (requiring ICU within two weeks of diagnosis, or died within sixty days) displayed an altered physiological response to hypoxaemia, and as such whether clinicians should be reassured, concerned, or feel equivocal regarding a reduced physiological response to hypoxaemia.

Methods

We performed a single-centre, retrospective, observational cohort study of adult patients admitted with suspected or confirmed COVID-19 to Nottingham University Hospitals NHS Trust, a large acute hospital Trust serving the East Midlands, UK.

Data for all patients aged eighteen or above admitted into hospital with suspected COVID-19 from 21st February 2020 (the date of disease onset of the first known case) until 31st August 2021 were extracted from the available electronic records (System C's *Medway* and Nervecentre Software's *Next Generation EPR*) with the use of an enterprise data warehouse. Patients were included in the COVID-19 cohort if they had a positive PCR test within ten days of being initially suspected, and the non-COVID-19 cohort all patients with negative PCR results. We excluded individuals who were not considered suitable candidates for escalation to ICU by their treating medical team.

We collected all nursing observations (simultaneously recorded heart rate, blood pressure, temperature, respiratory rate, peripheral oxygen saturation SpO_2, and oxygen delivery) from the point at which each patient was first suspected of having COVID-19, or positive SARS-CoV-2 PCR test, for fourteen days or until admission to intensive care, discharge home, or inpatient death if sooner. Patient outcomes (admission to ICU within fourteen days, and all-cause mortality within sixty days) and primary coded diagnosis for this admission were extracted from the same data. Heart rate, blood pressure, respiratory rate, and oxygen saturations were Winsorized to within five standard deviations of the mean to account for outliers as a consequence of misrecording[21]. Where not documented explicitly, fraction of inspired oxygen (FiO_2) was computed based on recorded oxygen flow rate and oxygen delivery device in use, and the SpO_2/FiO_2 ratio and ROX index calculated.

To assess for different response to hypoxaemia between cohorts, we modelled the observed physiological variables (respiratory rate, heart rate, systolic blood pressure, and temperature) as dependent on hypoxaemia – either peripheral oxygen saturations (absolute hypoxaemia) or SFR (relative hypoxaemia) – and COVID-19 status using a linear mixed effects model[22], adjusting for patient age and ethnicity, with a patient-level random intercept to account for repeated measurements from individual patients, and an interaction term between COVID-19 status and hypoxaemia. We excluded recordings with oxygen saturations above 92% or where supplemental oxygen was not administered, and in those undergoing palliation.

In order to assess whether "happiness" – impaired physiological response to hypoxaemia – was associated with poorer outcomes we repeated the analysis in the confirmed COVID-19 cohort alone,

modelling physiological response to absolute and relative hypoxaemia stratified by outcomes with an interaction term between hypoxaemia and outcome.

All data were analysed using *R* 4.0.4. Packages used are provided in the supplementary materials. Parametric variables were compared using Welch Two-sample *t*-test; non-parametric using Asymptotic Wilcoxon-Mann-Whitney test and medians calculated using Wilcoxon signed rank test with continuity correction. Wald 95% confidence intervals and p-values for mixed models are based on conditional F-tests with Kenward-Roger approximations. Full outputs from all models are included in the supplementary materials.

Approval for this work was approved by the Nottingham University Hospitals Clinical Effectiveness Team (reference 21-649C) and Caldicott Guardian (Data Protection Impact Assessment reference 436), and the National Health Service Health Research Authority (REC: 20/WM/0142, project ID: 282490, amendment No. SA02 20/07/21). The Health Reference Authority confirmed that individual patient consent was not required.

Results

The final dataset (table 1) contained 14,214 complete observations across 1,586 patients. 1,195 (75%) tested positive for COVID-19 within ten days of symptom onset, and represent the COVID-19 cohort (11,199 observations). Data from the remaining 391 patients who tested negative for COVID-19 infection were used as the comparison cohort (3,015 observations). Primary admission diagnoses for the non-COVID-19 cohort are included in the supplementary material.

	COVID-19 infection	**No COVID-19 infection**
n	1,195	391
Age[1]	58 (48, 69)	68 (58, 76)
Gender: Male[2]	718 (60%)	205 (52%)
Ethnicity:[2]		
White	680 (57%)	301 (77%)
Mixed	11 (0.9%)	<5 (<1.2%)
Asian	93 (7.8%)	8 (2.0%)
Black	62 (5.1%)	9 (2.3%)
Other	33 (2.8%)	<5 (<1.2%)
Not recorded	316 (26%)	69 (18%)
Worst outcomes[2]:		
Ward survivor to 60 days*	734 (61%)	264 (68%)
ICU within 14 days**	274 (23%)	56 (14%)
Death within 60 days	187 (16%)	71 (18%)

[1]Median (IQR), [2]n (%)
*Ward only/discharged within 14 days, survived to 60 days follow up
**Admitted to ICU within 14 days, survived to 60 days follow up

Table 1: Cohort demographics and outcomes

The COVID-19 cohort had a significantly higher respiratory rate, lower heart rate, and higher temperature than the no COVID-19 infection group (table 2, figure 1). Median absolute oxygen saturations were 0.6% higher in COVID-19 patients (95% CI 0.6 – 0.7), but COVID-19 patients were more relatively hypoxaemic with SFR 55 (95% CI 53 – 57) units lower than the non-COVID-19 cohort. COVID-19 patients also had a ROX index 3.1 (95% CI 3.0 – 3.3) min^{-1} lower, i.e. had a higher respiratory rate for any given degree of relative hypoxia.

	COVID-19 infection	**No COVID-19 infection**	**Difference (95% CI)**	**P-value**
Total observations	11,199	3,015		
Oxygen saturations[1]	91 (90-92)	90 (89, 92)	-0.6 (-0.7 to -0.6)	<0.001
Respiratory rate[2]	22 (5)	20 (4)	-1.2 (-1.4 to -1.0)	<0.001
Heart rate[2]	84 (16)	90 (16)	5.9 (5.3 – 6.6)	<0.001
Systolic blood pressure[2]	128 (20)	127 (22)	-0.3 (-1.2 – 0.5)	0. 500
Temperature[2]	36.8 (0.6)	36.7 (0.5)	-0.1 (-0.2 to -0.1)	<0.001
SFR[1]	258 (220-329)	317 (257-371)	55 (53 – 57)	<0.001
ROX[2]	12.6 (5.0)	15.7 (4.5)	3.1 (3.0 – 3.3)	<0.001

[1]Median (IQR); Wilcoxon-Mann-Whitney test
[2]Mean (SD); Welch Two-sample T-test

Table 2: Average unadjusted physiological variables by cohort

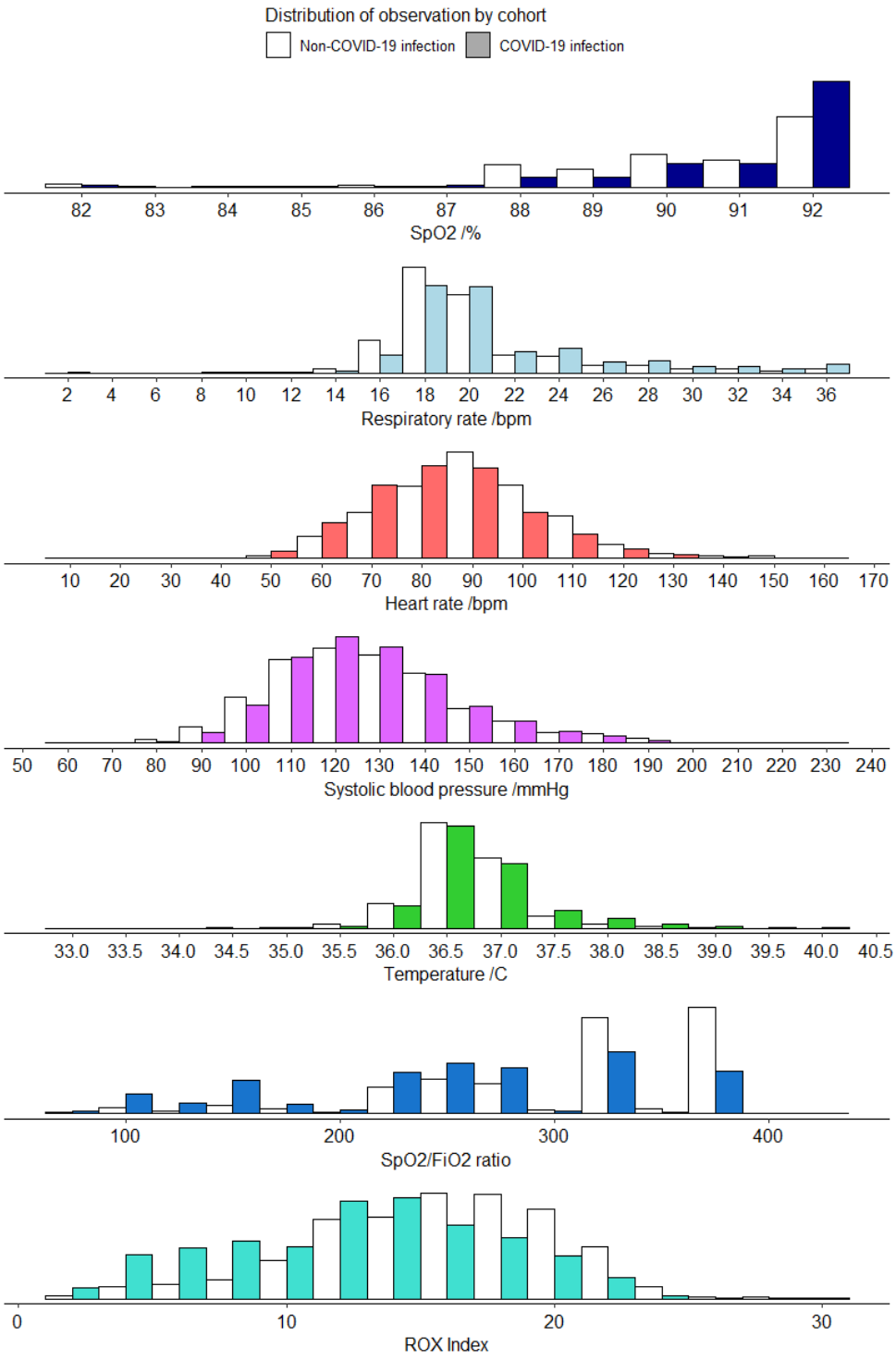

Figure 1: Frequency distributions of observations in hypoxaemic patients (defined by SpO2 ≤ 92 and requiring supplemental oxygen) by infection cohort (filled COVID-19 infection, unfilled no COVID-19 infection).

Physiological response to hypoxia between disease states

On average across all patients we observed a 0.3 breath per minute (Bpm) increase in respiratory rate with each 1% decrease in SpO_2 (95% confidence interval 0.3 – 0.4, p<0.001). COVID patients had a higher overall respiratory rate (0.8 Bpm, 0.3 – 1.3, p=0.001) for any degree of absolute hypoxaemia when compared to hypoxaemic respiratory failure of other causes (figure 2).

Similarly, there was a 0.1 Bpm increase in respiratory rate for each 10 unit decrease in SFR (0.1 – 0.1, p<0.001) in all patients, but with no significant difference between groups in response to relative hypoxaemia. However, COVID-19 patients additionally displayed a 0.1 Bpm (0.1 – 0.1, p<0.001) increase for each 10 unit fall in SFR when compared to hypoxic respiratory failure of other causes.

There was substantial residual inter- and intra-patient variability in the respiratory rate response to absolute (standard deviation 3.5 and 3.2 bpm respectively) and relative (standard deviation 3.2 and 3.2 bpm respectively) hypoxaemia.

Heart rate increased with both absolute and relative hypoxaemia (p<0.001), and COVID-19 patients had a 6.8 beat per minute (bmp) lower heart rate (5.1 – 8.5, p<0.001) at all levels of oxygen saturation and a 0.1 bpm (0.0 – 0.2, p=0.009) lower heart rate for each 10 unit decrease in SRF than non-COVID-19 patients.

Average systolic blood pressure increased by 0.3 mmHg (0.1 – 0.6, p=0.042) for each 1% decrease in oxygen saturations across all patients, with no difference between patients with and without COVID-19 (p=0.241), and no relationship with relative hypoxaemia (p=0.295). There was no association between temperature and absolute (p=0.995) or relative (p=0.458) hypoxaemia, but patients with COVID-19 had an average temperature 0.1°C higher (0.1 – 0.2, p<0.001). Intra- and inter-patient variability remained substantial for all three observations (see supplementary material and figure 2).

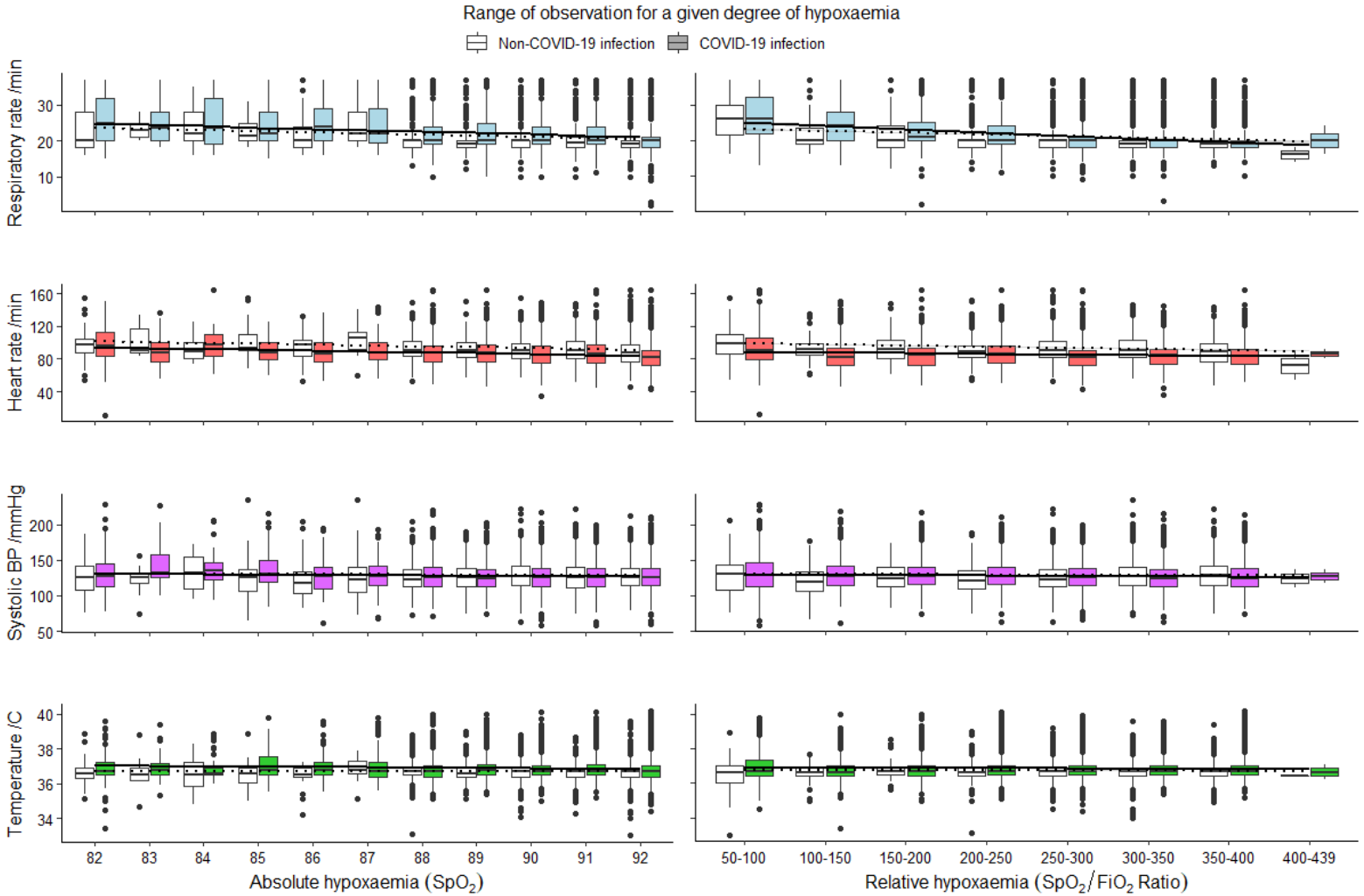

Figure 2: Association between degree of hypoxaemia (absolute left, and relative right) and physiological response stratified by COVID-19 infection status (filled/solid COVID-19, unfilled/dashed non-COVID-19 respiratory failure). Boxplots reflect the range of the observations in our dataset, and regression lines model the expected value of the observation, for any given degree of hypoxaemia.

Therefore in patients with severe absolute hypoxaemia (blood oxygen saturation of 85%), individuals with COVID-19 had on average a respiratory rate 1 (0 – 2) Bpm higher, heart rate 7 (4 – 10) bpm lower, and temperature 0.3 (0.1 – 0.4) °C higher than those without COVID-19. Similarly, in patients with severe relative hypoxaemia (SFR 100), individuals with COVID-19 had on average a respiratory rate 2 (1 – 3) Bpm higher, heart rate 10 (7 – 13) bpm lower, and temperature 0.2 (0.0 – 0.3) °C higher than those without COVID-19. There was no significant difference in systolic blood pressure.

The ROX index was 2.08 min^{-1} lower (1.56 – 2.61, $p<0.001$) in the COVID-19 cohort when adjusted for age and ethnicity, i.e. COVID-19 patients displayed a higher respiratory rate across all degrees of relative hypoxaemia. Residual inter- and intra-patient standard deviations were 3.98 and 3.31 respectively.

Physiological response to hypoxia and link to outcomes in COVID-19

Of the confirmed COVID-19 patients, 799 patients (67%) were not escalated to ICU within fourteen days of symptom onset, despite hypoxaemia and eligibility for escalation. Of the 396 (33%) admitted to ICU, 274 (69%) survived their ICU stay (to sixty day follow up) and 122 (31%) died within sixty days of symptom onset.

Those who were admitted to ICU had a more pronounced relative and absolute hypoxaemia and higher respiratory and heart rates than patients who did not go to ICU within fourteen days. Similarly, those who died had a more severe relative and absolute hypoxaemia and a higher respiratory rate than those who survived ICU to sixty days (table 3).

After adjusting for age and ethnicity, on average across all COVID-19 patients those admitted to ICU within fourteen days had a 3.0 Bpm (2.5 to 3.5, $p<0.001$), and those who died 4.0 Bpm (3.4 to 4.6, $p<0.001$), higher respiratory rate than ward survivors. ICU admissions and deaths both additionally displayed a more pronounced response to absolute (0.2 Bpm increase for every 1% fall in SpO2, 0.1 – 0.3; and 0.2 Bpm, 0.1 – 0.3, respectively, $p<0.001$) and relative (0.1 Bpm increase for every 10 unit fall in SFR, 0.1 – 0.2; and 0.1 Bpm, 0.1 – 0.2 respectively, $p<0.001$) hypoxaemia. There was once again substantial residual inter- and intra-patient variability in the respiratory rate response to absolute (standard deviation 3.1 and 3.4 bpm) and relative (2.9 and 3.3 bpm) hypoxaemia.

COVID-19 patients admitted to ICU or dying within sixty days of diagnosis also had a more pronounced tachycardia in response to absolute and relative hypoxaemia, with a further increase of 0.2 bpm (0.1 to 0.3, $p<0.001$) per 10 unit fall in SFR in ICU survivors to sixty days, and 0.1 bpm (0.0 to 0.2, $p=0.011$) in those dying. There was no difference in systolic blood pressure or temperature (figure 3).

	Ward survivors*	ICU within 14 days	Difference (95% CI)[3]	p-value[3]	60 day mortality	Difference (95% CI)[4]	p-value[4]
Total observations	6,399	2,707			2,093		
Oxygen saturation[1]	92 (91-92)	91 (90-92)	-0.4 (-0.5 to -0.3)	<0.001	90 (89-92)	-0.8 (-1.0 to -0.7)	<0.001
Respiratory rate[2]	20 (4)	23 (5)	2.7 (2.4 – 2.9)	<0.001	24 (6)	0.5 (0.1 to 0.8)	0.005
Heart rate[2]	82 (15)	88 (16)	5.5 (4.8 – 6.2)	<0.001	86 (17)	-1.7 (-2.7 to -0.8)	<0.001
SBP[2]	128 (19)	128 (19)	0.0 (-0.9 – 0.8)	>0.900	129 (24)	1.4 (0.2 – 2.6)	0.027
Temperature[2]	36.8 (0.6)	36.9 (0.7)	0.1 (0.1 – 0.2)	<0.001	36.8	-0.1 (-0.1 to -0.0)	<0.001
SFR[1]	288 (249-329)	236 (153-288)	-55 (-51 to -58)	<0.001	204 (136-263)	-24 (-16 to -29)	<0.001
ROX[2]	14.3 (4.3)	10.9 (5.0)	-3.5 (-3.7 to -3.3)	<0.001	9.6 (4.9)	-1.3 (-1.6 to -1.0)	<0.001

[1]Median (IQR); Wilcoxon-Mann-Whitney test
[2]Mean (SD); Welch Two-sample T-test
[3]Compared to ward-based survivors
[4]Compared to ICU survivors

Table 3: Average unadjusted physiological variables in COVID-19 cohort, stratified by worst outcome. Increasing severity of outcomes were associated with higher respiratory rate, worsening absolute and relative hypoxaemia, and lower ROX index (higher respiratory rate for given degree of relative hypoxaemia).

Therefore in COVID-19 patients with severe absolute hypoxaemia (blood oxygen saturation of 85%), individuals who required ICU had on average a respiratory rate 4 (3 – 5) Bpm higher, and heart rate 7 (3 – 11) bpm higher, than those who survived to sixty days with ward-based care alone. Patients who died within sixty days had on average a respiratory rate 5 (4 – 5) Bpm higher, and heart rate 8 (4 – 12) bpm higher than those who survived with ward-based care. Similarly, in COVID-19 patients with severe relative hypoxaemia (SFR 100), individuals who required ICU had on average a respiratory rate 4 (3 – 5) Bpm higher, and heart rate 8 (5 – 12) bpm higher, than those who survived with ward-based care. Patients who died within sixty days had on average a respiratory rate 5 (4 – 6) Bpm higher, and heart rate 10 (6 – 14) bpm higher than those who survived with ward-based care. There was no significant difference in systolic blood pressure.

The ROX index was significantly lower in those who were admitted to ICU (4.22 lower, 3.71 to 4.73, $p<0.001$) and those who died (6.13 lower, 5.54 to 6.72, $p<0.001$) when adjusted for age and ethnicity than in those surviving to sixty days with ward based care, i.e. those admitted to ICU or dying within sixty days displayed a higher respiratory rate across all degrees of relative hypoxaemia. Residual inter- and intra-patient standard deviations were 3.24 and 3.37 respectively.

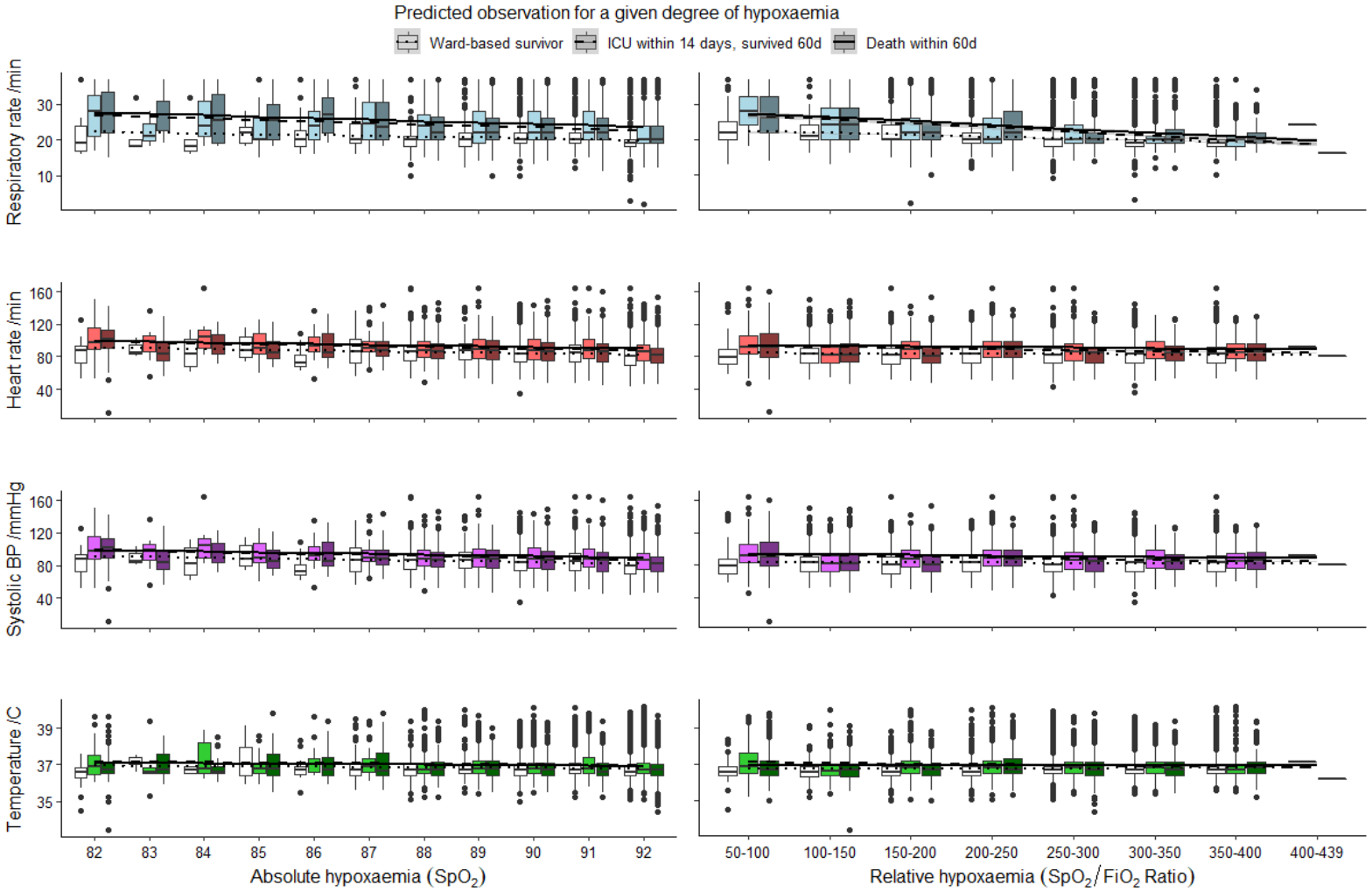

Figure 3: Association between degree of absolute (left) and relative (right) hypoxaemia and physiological response in COVID-19 patients, stratified by outcome. Boxplots reflect the range of the observations in our dataset for patients with COVID-19 experiencing the three outcomes, and regression lines model the expected value of the observation for a patient experiencing said outcome, for any given degree of hypoxaemia

Discussion

Our data demonstrates that although “asymptomatic” hypoxaemia may be a phenomenon in any individual patient with respiratory failure, a physiological phenotype of “happiness” is no more frequently observed in those with SARS-CoV-2 infection than in hypoxaemic respiratory failure of other causes. Indeed, patients with hypoxaemic respiratory failure as a consequence of COVID-19 have on average a higher respiratory rate than patients without COVID-19 infection for any given degree of absolute or relative hypoxaemia, albeit with substantial variability in the response within and between individual patients in both cohorts. Our results therefore refute the notion of COVID-19 infected patients being any more “happy” with hypoxaemia than non-COVID-19 patients, with an overall lower ROX in COVID-19 patients demonstrating a more pronounced physiological response in this cohort to hypoxaemia for all degrees of relative hypoxaemia.

We also found that within the COVID-19 cohort, poorer outcomes were associated with patients who exhibit a more physiologically “unhappy” phenotype in terms of an elevated respiratory and heart rates across all degrees of hypoxaemia. This too is supported by the ROX index being lower in those with poorer outcomes, reflecting an association between higher respiratory rate for any given degree of relative hypoxaemia and risk of ICU admission or death.

The ROX index, initially designed to predict failure of non-invasive oxygenation in ICU and so utilising only bedside observations, has been applied to patients with COVID-19 in ICU to assess the severity of their hypoxic respiratory failure[17–20,23] and in correlation with radiological findings[24], with values ranging from 3[25] to 5.99[23] (including the non-COVID discriminator of 4.99[26]) being considered the optimal cut-off to signify requirement for intubation in the ICU setting. By considering ROX as a marker of respiratory response to relative hypoxaemia, our study not only supports the use of this index in predicting adverse outcomes in ICU, but suggests that it may have utility for detecting patients outside of ICU at risk of deterioration with exaggerated respiratory responses to lower degrees of relative hypoxaemia, as it can be derived in a straightforward manner from nursing observations

The mechanism of severe hypoxaemia in COVID-19[27] remains poorly understood[28–30], with some authors considering that hypoxaemia with limited physiological response represents a distinct phenotype of COVID-19[31]. Hypothesised causes include: intrapulmonary shunting[32] as a result of oedema and atelectasis[30], thrombocclusive disease[33], or vascular angiogenesis[34]; loss of lung perfusion regulation[35] and excess nitric oxide production[36]; alterations of the oxyhaemoglobin dissociation curve (OHDC) due to COIVD-19 directly[37–40] or secondary to hypocapnoea due from hyperventilation[41]; secondary antiphospholipid syndrome[42]; alterations in central and peripheral chemoreceptor response due to ACE2 receptor modulation[43,44] or mitochondrial injury[2]; and virus-related autonomic interoception[45].

The suggestion that “happy hypoxia” reflects a low compliance subtype of the disease has been contested[46]. Although increasing estimated shunt fraction has been demonstrated to be associated with mortality[47], this simply explains the degree of relative hypoxaemia observed in our patient group, with limited evidence for any form of biochemical or ventilatory disease subtypes prior to the onset of mechanical ventilation in those requiring ICU[48]. Furthermore, dyspnoea is not necessarily produced as a consequence of acute hypoxemia, since respiratory centre activity in the absence of severe derangements of the respiratory mechanics is relatively low meaning that ventilatory demands continue to be met. As such, dyspnoea – or indeed an elevated respiratory rate – would instead reflect respiratory compromise as a consequence of the disease, rather than a consequence of the severe hypoxaemia[49].

Our study does have a number of limitations. Although the case fatality rate was similar between COVID-19 and non-COVID-19 patients, a higher proportion of COVID-19 patients required admission to ICU, which may bias observations towards an overall “sicker” population of patients given that the COVID-19 cohort had a more pronounced relative hypoxaemia over all observations. The COVID-19 infected cohort was also younger, and more likely to have an ethnicity other than white, which may limit generalisability.

Similarly, although we can assume that most, if not all, hypoxaemic patients with confirmed SARS-CoV-2 infection and within fourteen days of disease onset are in

hospital as a consequence of COVID-19, the non-COVID-19 group likely represents a more heterogeneous group of illnesses which cannot be subdivided based on this pseudonymised clinical dataset beyond their principle coded diagnosis for that admission. This was intentional, as we wished to compare the physiological response of patients with identical degrees of hypoxaemic respiratory failure but differing underlying disease processes, however caution should be taken when extrapolating results to non-COVID-19 patients. Nevertheless, 53% of patients presented with an infective cause, 8% with a primary respiratory condition, and 4% with features of right-sided cardiac failure or pulmonary hypertension, so the cohort does bear similar pathophysiological features to those seen in severe COVID-19 pneumonitis.

For this analysis we intentionally relied solely on the use of routinely collected observations to quantify physiological response to hypoxaemia, rather than the subjective assessment of work of breathing recorded by medical or nursing staff, as this was poorly documented in our dataset. However, both respiratory rate[50] and peripheral oxygen saturations[51] are also prone to systematic errors in their recording. We also did not include other markers of severity of illness (such as inflammatory markers and radiological findings[52]), and in the interests of using a larger cohort of patients and making the results generalizable to clinicians assessing patients outside of ICU, we relied on bedside observations rather than correlating hypoxaemia with PaO_2 from invasive blood gas results, which fails to account for possible disruption to the oxyhaemoglobin dissociation curve in COVID-19[38] and acknowledge that PaO_2, rather than SaO_2, drives ventilation through stimulation of the carotid bodies in hypoxaemia. Additionally, although we have adjusted the physiological response to hypoxaemia for age[53] and ethnicity, we have not adjusted results for the presence of cardiorespiratory comorbidities or those known to impact on the response to hypoxaemia[54].

Finally, although we have used the ROX index for distinguishing between cohorts in their respiratory rate response to hypoxaemia, and as such potentially reflecting the need for ICU admission, this analysis is not sufficient to identify clinically useful thresholds for this. As it was designed to focus on identifying the existence and relevance of asymptomatic hypoxaemia, in this analysis we have treated ROX as a continuous variable. We are therefore hesitant to identify a threshold value for

adverse outcomes from this study without a larger cohort that can be used for validation, as to do would risk overfitting our cohort and lead to potentially misleading results, while simultaneously losing clinically relevant information regarding risk of deterioration gained from treating ROX as a continuous measure. As such further work is necessary before we can confidently recommend the use of the ROX index outside of predicting need for intubation in ICU.

Conclusion

Patients with confirmed SARS-CoV-2 infection have a more pronounced physiological response to hypoxaemia (i.e. elevated respiratory rate) to any degree of hypoxaemia than non-COVID-19 patients, after adjusting for age and ethnicity. Furthermore, a more disturbed physiological response to hypoxaemia in COVID-19 (i.e. elevated respiratory rate) was associated with poorer outcomes for any degree of absolute or relative hypoxaemia. Consequently we agree that there are 'no compelling pathophysiological reasons at present to support a therapeutic approach for patients with respiratory failure due to SARS-CoV-2 that is different from proven standards of care in ARDS'[1], nor to support the current paradigm in COVID-19 management that physiological "happiness" in response to hypoxaemia is associated with poorer outcomes[55].

Having worked through the COVID-19 pandemic we recognise the clinical picture of the "happy hypoxic" from personal experience. However, our data suggest that this is simply the recognition of individual outliers in terms of their respiratory response to hypoxaemia, albeit in the context of an unusually large number of patients with extreme degrees of hypoxaemia as a consequence of ARDS, rather than as a direct result of COVID-19 infection per se, and that witnessing the "expected" physiological response to severe hypoxaemia is a stronger predictor of poor outcomes.

Declarations

Ethical approval

Approval for this work was granted via the Nottingham University Hospitals Clinical Effectiveness Team (audit 21-649C) and Caldicott Guardian (Data Protection Impact Assessment reference 436), and the National Health Service Health Research Authority (REC: 20/WM/0142, project ID: 282490, amendment No. SA02 20/07/21).

Consent for publication

The Health Reference Authority confirmed that individual patient consent was not required.

Availability of data and materials

Summary data that support the findings of this study and analysis code are available on reasonable request from the corresponding author. The data are not publicly available due to containing information that could compromise participant privacy by nature of being an active clinical dataset.

Competing interests

None of the authors have conflicts of interest to declare

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Authors' contributions

NP, AF, DS, and CC conceived the report. TC, JW, and CC coordinated collection and access to the data, and take responsibility for its integrity. NP and CC performed data analysed. NP drafted the report. All authors critically revised the manuscript, and approved its publication. CC is the guarantor.

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