Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Lymphocyte count and partial pressure of oxygen can be used as a screening test for COVID-19 in secondary care

Dear editor

In United Kingdom (UK) secondary care, identification of SARS-CoV-2 – aetiological agent for Coronavirus Disease 2019 (COVID-19) – is reliant on polymerase chain reaction (PCR) testing of nasopharyngeal swabs. Whilst PCR testing capabilities and turnaround times have improved nationally, results are rarely available when critical cohorting and treatment decisions are made thus delaying appropriate management and exposing susceptible patients and staff to patients with COVID-19. A quick, clinically applicable screening test in secondary care is needed on admission to help in the appropriate isolation and cohorting of patients, especially with the increasing prevalence of COVID-19 and the impending seasonal increase in other respiratory tract infections. As respiratory symptoms and lymphopaenia secondary to COVID-19 have been well described previously[1–3], we performed a study of consecutive patients to determine whether lymphocyte count and partial pressure of oxygen (pO2) on admission can be used as a screening test for COVID-19 in UK secondary care.

All adult patients consecutively admitted to two designated COVID-19 wards within Darent Valley Hospital (Kent, UK) between 19th March and 30th April were included in this retrospective study. Patients were admitted to these wards based on the presence of respiratory symptoms (i.e. cough, shortness of breath, fever, etc.) or radiological evidence of pneumonia. Fever was defined as a temperature of 37.8 °C or higher. COVID-19 was confirmed by the presence of SARS-CoV-2 RNA in nasopharyngeal swabs and reported by a UK Public Health England Reference Laboratory (UK PHE Southampton), with data collected from the hospital’s electronic record system. An electronic form was designed to collect clinical, laboratory, and radiological data on admission. Optimum cut-off points for pO2 and lymphocyte count were determined by Youden’s Index [4]. A two by two table was used to calculate sensitivity, specificity, positive predictive value (PPV) and a negative predictive value (NPV) of the screening tests. True PPV and NPV with prevalence considered were calculated with the following equations:

\[
PPV = \frac{(\text{sensitivity} \times \text{prevalence})}{(\text{sensitivity} \times \text{prevalence}) + (1 - \text{specificity}) \times (1 - \text{prevalence})}
\]

\[
NPV = \frac{\text{specificity} \times (1 - \text{prevalence})}{(\text{specificity} \times (1 - \text{prevalence})) + (1 - \text{sensitivity}) \times \text{prevalence}}
\]

Data manipulation and analysis was performed using RStudio, version 4.0.0 (RStudio, Boston, MA).

During the study period, 253 consecutive patients were admitted to the cohort wards, with 145 (59.4%) patients testing positive for COVID-19. 157 (61.3%) patients were male, with a median age of 67 years (IQR 54–80 years). COVID-19 patients were more likely to have fever and cough on admission (Table 1). 20 patients (7.8%) had no significant past medical history. Patients with COVID-19 had a lower pO2 (p = 0.001) and lymphocyte count (p = 0.006) on admission. This is supported by univariate analyses which showed that the odds for a positive SARS-CoV-2 test were higher in patients with a lower pO2 (OR 0.77, 95% CI 0.64–0.90, p = 0.002) and lymphocyte count (OR 0.61, 95% CI 0.41–0.88, p = 0.01) (Table 2).

A pO2 of 9.0 kPa and a lymphocyte count of 1.0 × 10^9 cells/L were optimum cut-off points. A pO2 of 9.0 kPa has a sensitivity of 58.8% and a specificity of 68.8% (PPV 77.0%, NPV 48.1%). A lymphocyte count of 1.0 × 10^9 cells has a sensitivity of 60.8% and specificity 53.7% (PPV 70.2%, NPV 43.3%). The combination of both markers improves the specificity of 83.3%, with a sensitivity of 43.9% (PPV 82.7%, NPV 45.5%). This improves marginally in a sub-analysis of patients with cough and fever, with a specificity of 85.3% and sensitivity of 44.3% (PPV 87.5%, NPV 39.7%). Assuming the UK COVID-19 prevalence is approximately 0.27% [5], the NPV of a pO2 9.0 kPa and a lymphocyte count of 1.0 × 10^9 cells/L increases to 99.8% with the PPV decreasing to 0.01%.

We’ve shown that a combination of pO2 and lymphocyte count can be used as a screening test for COVID-19 in symptomatic patients. This likely reflects the fact that patients with COVID-19 predominantly presented with significant hypoxaemia with a low lymphocyte count on admission. Both pO2 and lymphocyte count has good specificity and negative predictive value compared to each individual marker used in isolation, especially when COVID-19 prevalence is considered. Given the high NPV, the combination of pO2 and lymphocyte count can be used as a “rule-out” test, i.e., a pO2 > 9.0 kPa and lymphocyte count >1.0 × 10^9 cells/L would likely mean a negative SARS-CoV-2 PCR test. This would be particularly useful when cohorting patients on admission. Patients with pO2 > 9.0 kPa and lymphocyte count >1.0 × 10^9 cells/L have a low likelihood for SARS-CoV-2 positivity on admission and can be separated from patients with confirmed COVID-19. Patients with a pO2 < 9.0 kPa and lymphocyte count <1.0 × 10^9 cells/L should be treated as presumed positive until the confirmation of a SARS-CoV-2 PCR result.
If the prevalence of COVID-19 increases, the PPV of pO2 and lymphocyte count will also increase while the NPV decreases. However, it is important to note that NPV will remain more than 80% if the prevalence of COVID-19 remains less than 25%, signifying its utility as a "rule-out" test.

This is to our knowledge the first study conducted in a UK district general hospital investigating the use of pO2 and lymphocyte count as a screening test for COVID-19. Many studies have investigated prediction models for COVID-19 [6–8], but these are often difficult to implement in practice. Arterial pO2 levels and lymphocyte counts are quick to obtain and readily available in UK secondary care settings, making it easier to use in routine practice. Our study has the following limitations: Patients may have been pre-selected based on symptom severity prior to admission to the designated COVID-19 wards and therefore we observed more patients with low pO2 within this cohort. Furthermore, the use of pO2 and lymphocyte count as a screening test for COVID-19 is only applicable in patients with respiratory symptoms, as it is likely that asymptomatic patients or those with primarily non-respiratory manifestations would not have low pO2 on admission.

In summary, pO2 and lymphocyte count can be used as a "rule-out" screening test for COVID-19 with a good NPV. Our findings provide a clinically applicable screening test which can aid healthcare professionals in resource limited settings or even during a resurgence of cases in more developed settings when making treatment and cohorting decisions for COVID-19.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Acknowledgements**

We would like to express our sincere gratitude to Dr. Anthony Raharja who assisted in data collection as well as Dr. Jonathan Kwan, Division Director of Acute Services, Darent Valley Hospital.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

### Table 1
Demographic, clinical, and laboratory characteristics of patients on admission.

| Clinical Characteristics | Negative | Positive | P-value |
|--------------------------|----------|----------|---------|
| N (%)                    | 108 (44.4) | 145 (59.6) | 0.69    |
| Male (n (%))             | 64 (92.4)  | 93 (64.1)  |         |
| Age                      | 69 (54–80) | 66 (53–80) | 0.53    |
| Duration of Symptoms (days) | 3 (2–7)  | 7 (1–7)   | 0.071   |
| Past Medical History (n (%)) | 37 (34.2) | 59 (40.6) | 0.36    |
| Hypertension             | 27 (25.0)  | 29 (20.0)  | 0.36    |
| Diabetes                 | 13 (12.0)   | 19 (13.1)  | 0.85    |
| Ischaemic Heart Disease  | 23 (21.3)   | 16 (11.3)  | 0.033   |
| Chronic Obstructive Pulmonary Disease | 16 (14.8) | 19 (13.1) | 0.715   |
| Cancer                   | 4 (3.7)    | 10 (6.9)   | 0.162   |
| Chronic Kidney Disease   | 11 (10.1)   | 13 (9.0)   | 0.829   |
| Asthma                   | 9 (8.3)    | 17 (11.7)  | 0.41    |
| Stroke                   | 21 (19.4)   | 9 (6.2)    | 0.017   |
| Congestive Cardiac Failure | 6 (5.6)   | 13 (9.0)   | 0.345   |
| Dementia                 | 6 (5.6)    | 16 (11.0)  | 0.177   |
| Contact with COVID-19 cases | 6 (5.6)   | 16 (11.0) | 0.177   |
| **Laboratory Characteristics** |          |          |         |
| Haemoglobin (g/L)        | 130 (120–146) | 131 (114–144) | 0.177   |
| C-reactive Protein (mg/l) | 87 (23–176) | 115 (47–175) | 0.101   |
| Lymphocyte Count (10^9 cells/L) | 1.1 (0.7–1.6) | 0.8 (0.6–1.3) | 0.006   |
| Neutrophil Count (10^9 cells/L) | 8.0 (4.8–11.3) | 5.4 (4.0–7.8) | 0.001   |
| Platelet Count (10^9 cells/L) | 211 (163–280) | 257 (191–325) | 0.001   |
| Creatinine (umol/L)      | 89 (67–135) | 83 (69–124) | 0.433   |
| pO2 (kPa)                | 9.2 (7.9–10.8) | 8.1 (7.1–9.1) | 0.001   |
| pCO2 (kPa)               | 4.5 (3.9–5.2) | 4.3 (3.8–4.7) | 0.058   |
| pH                       | 7.44 (7.40–7.49) | 7.46 (7.43–7.50) | 0.059   |
| Radiological evidence of pneumonia (n (%)) | 56 (52.3) | 110 (75.9) | 0.0001  |

Footnotes: Percentages were used to describe categorised data. Median and interquartile range (IQR) were used to report continuous data. Mann-Whitney U test was used to compare continuous data and Fisher’s exact test is used to compare categorical data. Statistical significance was set at p < 0.05.

### Table 2
Risk factors for a positive COVID-19 test.

|                      | Univariate OR (95% CI) | Multivariate OR (95% CI) | P-value (univariate) | P-value (multivariate) |
|----------------------|------------------------|--------------------------|----------------------|------------------------|
| Age                  | 1.00 (0.98–1.01)       |                          | 0.643                |                        |
| Sex                  | 1.08 (0.64–1.82)       |                          | 0.76                 |                        |
| Hypertension         | 1.31 (0.79–2.21)       |                          | 0.298                |                        |
| Diabetes             | 0.84 (0.43–1.65)       |                          | 0.34                 |                        |
| IHD                  | 1.1 (0.52–2.39)        |                          | 0.88                 |                        |
| COPD                 | 0.46 (0.23–0.91)       |                          | 0.027                |                        |
| Dyspnoea             | 1.42 (0.85–2.40)       |                          | 0.183                |                        |
| Cough                | 2.35 (1.42–3.95)       | 2.00 (0.85–4.69)         | 0.001                | 0.11                   |
| Fever                | 2.85 (1.71–4.82)       | 2.80 (1.19–6.62)         | <0.0001              | 0.01                   |
| pO2                  | 0.77 (0.64–0.90)       | 0.78 (0.64–0.95)         | 0.002                | 0.01                   |
| pCO2                 | 0.71 (0.52–0.94)       | 0.74 (0.50–1.05)         | 0.02                 | 0.11                   |
| Lymphocyte count     | 0.61 (0.41–0.88)       | 0.91 (0.52–1.60)         | 0.01                 | 0.75                   |
| Neutrophil count     | 0.98 (0.95–1.01)       |                          | 0.185                |                        |
| C-reactive Protein   | 1.00 (0.99–1.00)       |                          | 0.843                |                        |
| Platelet Count       | 1.00 (0.99–1.00)       |                          | 0.008                |                        |

Footnotes: Both univariate analysis and multivariate analysis were performed using logistic regression. Variables with p < 0.05 are selected for multivariate analysis if deemed clinically relevant to the diagnosis of COVID-19. IHD, Ischaemic Heart Disease; COPD, Chronic Obstructive Pulmonary Disease; pO2, partial pressure of oxygen; pCO2, partial pressure of carbon dioxide.
References

1 Zhou Fei, Yu Ting, Du Ronghui, Fan Guohui, Liu Ying, Liu Zhibo, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395(10229):1054–62. https://doi.org/10.1016/S0140-6736(20)30566-3.

2 Chen Tao, Di Wu, Chen Huilong, Yan Weiming, Yang Danlei, Chen Guang, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2019;2020(368). https://doi.org/10.1136/bmj.m1091.

3 Richardson Safiya, Hirsch Jamie S, Narasimhan Mangala, Crawford James M, McGinn Thomas, Davidson Karina W, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized With COVID-19 in the New York City Area. JAMA 2020;323(20):2052–9. https://doi.org/10.1001/jama.2020.6775.

4 Youden WJ. Index for rating diagnostic tests. Cancer 1950;3(1):32–5. https://doi.org/10.1002/1097-0142(1950)3:1<32::aid-cncr2820030106>3.0.co;2-3.

5 Office for National Statistics. Coronavirus (COVID-19) infection survey pilot; 2020.

6 Feng Cong, Huang Zhi, Wang Lili, Chen Xin, Zhai Yongzhu, Zhu Feng, et al. A novel triage tool of artificial intelligence assisted diagnosis aid system for suspected COVID-19 pneumonia in fever clinics. MedRxiv 2020;2020(03). https://doi.org/10.1101/2020.03.20.20039099.

7 Sun Yinxiaohong, Koh Vanessa, Marimuthu Kalisvar, Ng Oon Tek, Young Barnaby, Vasoo Shawn, et al. Epidemiological and clinical predictors of COVID-19. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa222.

8 Jin Cheng, Chen Weixiang, Cao Yuxuan, Xu Zhanwei, Tan Zimeng, Zhang Xin, et al. Development and evaluation of an AI system for COVID-19 diagnosis. MedRxiv 2020. https://doi.org/10.1101/2020.03.20.20039813.