Robust, reproducible clinical patterns in hospitalised patients with COVID-19

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Abstract

Severe COVID-19 is characterised by fever, cough, and dyspnoea. Symptoms affecting other organ systems have been reported. The clinical associations of different patterns of symptoms can influence diagnostic and therapeutic decision-making: for example, significant differential therapeutic effects in sub-groups of patients with different severities of respiratory failure have already been reported for the only treatment so far shown to reduce mortality in COVID-19, dexamethasone.

We obtained structured clinical data on 68914 patients in the UK (the ISARIC Coronavirus Clinical Characterisation Consortium, 4C) and used a principled, unsupervised clustering approach to partition the first 33468 cases according to symptoms reported at recruitment. We validated our findings in a second group of 35446 cases recruited to ISARIC-4C, and in separate cohort of community cases.

A core symptom set of fever, cough, and dyspnoea co-occurred with additional symptoms in three patterns: fatigue and confusion, diarrhoea and vomiting, or productive cough. Presentations with a single reported symptom of dyspnoea or confusion were common, and a subgroup of patients reported few or no symptoms. Patients presenting with gastrointestinal symptoms were more commonly female, had a longer duration of symptoms before presentation, and had lower 30-day mortality. Patients presenting with confusion, with or without core symptoms, were older and had a higher unadjusted mortality. Symptom clusters were highly consistent in replication analysis using a further

35446 individuals subsequently recruited to ISARIC-4C. Similar patterns were externally verified in 4445 patients from a study of self-reported symptoms of mild disease.

The large scale of ISARIC-4C study enabled robust, granular discovery and replication of patient clusters. Clinical interpretation is necessary to determine which of these observations have practical utility. We propose that four patterns are usefully distinct from the core symptom groups: gastro-intestinal disease, productive cough, confusion, and pauci-symptomatic presentations. Importantly, each is associated with an in-hospital mortality which differs from that of patients with core symptoms. These observations deepen our understanding of COVID-19 and will influence clinical diagnosis, risk prediction, and future mechanistic and clinical studies.

Introduction

The recognition of clinical similarities between patients is a fundamental unit of medical progress. Grouping patients enables us to select appropriate diagnostic tests, predict response to therapy, and to prognosticate. Simple machine learning methods can reveal patterns in clinical symptoms[1] with diagnostic and therapeutic relevance.[2] Severe coronavirus-19 disease (COVID-19), that is, confirmed COVID-19 as the primary reason for hospitalisation, is characterised by a triad of symptoms: cough, fever and dyspnoea. However, it is clear that COVID-19 is not a homogeneous clinical entity. Important biological differences are likely to exist between patient subgroups, as is seen in other forms of critical illness including sepsis,[3] pancreatitis,[4] and dengue.[5] Remarkably, this is already evident for COVID-19: highly significant sub-group effects were seen in the first drug trial to demonstrate an improvement in mortality, dexamethasone.[6]

We employed unsupervised machine learning techniques in a large, prospective cohort of hospitalised patients with confirmed infection with SARS-CoV-2, to characterise the symptoms of severe COVID-19 and to identify clinical sub-groups.

Methods

Study design, setting, and population

The ISARIC Coronavirus Clinical Characterisation Consortium (4C) study is an ongoing prospective cohort study, involving 260 acute hospital sites in England, Scotland, and Wales.

The study builds on an international consensus protocol for investigation of new infectious diseases, the International Severe Acute Respiratory Infection Consortium/World Health Organisation Clinical Characterisation Protocol (ISARIC/WHO CCP),[7] designed to enable internationally-harmonised clinical research during outbreaks.[8] The protocol, revision history, case report form, information leaflets, consent forms, and details of the Independent Data and Material Access Committee are available at https://isaric4c.net. The UK study was approved by the South Central - Oxford C Research Ethics Committee (13/SC/0149) and by the Scotland A Research Ethics Committee (20/SS/0028). This study is reported in compliance with the STROBE guidelines.[9]

Patients included in the primary analysis were admitted to hospital between 6th February and 8th May, 2020. Inclusion criteria were all patients admitted to a participating hospital with laboratory proven or clinically highly suspected SARS-CoV-2 infection. Reverse transcription-PCR was the sole method of testing available during the study period. In the original CCP,[7] the inclusion of patients with clinically-suspected infection reflects the design of this study as a preparedness protocol where laboratory tests may not be available, but in the context of this outbreak in the UK, site training emphasised the importance of enrolling only laboratory-confirmed cases. Patients who were admitted to hospital for an unrelated condition but who subsequently tested positive for SARS-CoV-2 were also included.

Data collection

Data were collected on a case report form, developed by ISARIC and WHO in advance of this outbreak. From admission, data were uploaded to an electronic database (REDCap,

Vanderbilt University, US; hosted by University of Oxford, UK). We recorded demographic details as well as patient co-morbidities, in-hospital clinical course, treatments, and outcomes.

The presence or absence of a pre-defined list of symptoms was assessed at hospital admission. These were: fever, cough, productive cough, haemoptysis, dyspnoea, wheeze, chest wall in-drawing, chest pain, fatigue, myalgia, joint pain, vomiting, diarrhoea, abdominal pain, headache, confusion, seizures, lymphadenopathy, ear pain, sore throat, runny nose, conjunctivitis, rash, and skin ulceration.

Similarly, the presence of pre-defined co-morbidities was recorded. These were: asthma, diabetes (type 1 and type 2), chronic cardiac disease, chronic haematological disease, chronic kidney disease, chronic neurological disease, chronic pulmonary disease (excluding asthma), dementia, HIV, malignancy, malnutrition, mild liver disease, moderate or severe liver disease, obesity, chronic rheumatological disease, and smoking history.

Outcomes data were collected for admission to critical care (Intensive Care Unit or High Dependency Unit), the use of invasive mechanical ventilation (IMV), and in-hospital mortality.

Statistical analysis

Continuous data are summarised as median (inter-quartile range). Categorical data are summarized as frequency (percentage). Prevalence is reported as percentage (95%

confidence interval (CI)). Confidence intervals were calculated for a binomial proportion using the Clopper-Pearson exact method. We analysed data using R (R Core Team, Version 4.0.0, Vienna, Austria). P values <0.05 were deemed significant.

Missing data - Given the extraordinary circumstances in which this study was conducted there was a large amount of missing data. No attempt at multiple imputation was made. In respect of symptom data, in many cases the presence of a positive symptom(s) was recorded, with the remainder missing. Exploration of the structure of missing symptom data (**Supplementary Figure S1**) suggests that this did not occur at random. In such cases, missing symptoms were recoded as being absent. Patients with fully missing data were excluded from the analysis.

Symptom network analysis - To explore the relationship between the 25 recorded symptoms we fitted an Ising model, using L1-regularised logistic regression with model selection by Extended Bayesian Information criteria (EBIC),[10] using the R package *IsingFit*. A λ value of 10 was chosen to minimise spurious conditional dependencies. The partition of symptoms into communities was formalised using a short random walks method, with the R package *igraph*.[11]

Unsupervised partitional clustering - Symptom data for each patient, encoded as binary responses, were used to derive a Jaccard distance matrix. This was then supplied as the input to a k-medoids clustering algorithm. This is an unsupervised partitional algorithm that seeks to divide the sample into *k* clusters, where the arbitrary distance between any

individual case and the case chosen as the centre of a cluster (medoid) is minimised. In this study we used a variation of this algorithm, Clustering for Large Applications (CLARA), with the R package *cluster*.[12] CLARA, for the optimisation of computational runtime, performs iterations of k-medoids clustering on subsets of the data and selects the best performing result. We clustered 100 random sub-samples each consisting of approximately 10% of the analysed population (n=2500). Each sub-sample was used to select *k* medoid cases, after which every case in the dataset was assigned to the nearest medoid. The iteration in which the mean of the dissimilarities between cases and the nearest medoid was lowest was selected. Random sampling was performed deterministically to ensure consistency between our primary analysis and validation steps. Clustering was performed agnostic of patient demographics or outcome. The optimal number of clusters to specify to the algorithm was derived from a 'majority' assessment of three measures; total within sum of squares, average silhouette width, and gap statistic,[13] in which a parsimonious solution was preferred. To assess the stability of clusters, we employed a non-parametric bootstrap-based strategy.[14] This generated 1000 new datasets by randomly drawing samples from the initial dataset with replacement and applying the same clustering technique to each. Clustering results were then compared for each cluster identified in the primary analysis and the most similar cluster identified for each random re-sampling. A mean value for the Jaccard coefficient, for the sum of the comparisons, was generated for each cluster present in the primary analysis. As a sensitivity analysis, clustering was repeated on patients with only fully complete symptom data. Cluster allocations for individuals partitioned by both iterations were then compared using Cohen's kappa and simple percentage agreement with the R package *irr*.

Clustering validation - We performed two validations, one internal and one external. Internally, we used symptom data for patients enrolled to ISARIC CCP-UK after those included in the primary analysis and until 7th July, 2020. These data were processed and analysed as for the primary cohort. Missing data were treated in the same fashion. Externally, our clustering strategy was replicated independently in a sub-sample of users from the COVID Symptom Study app (developed by Zoe Global Ltd. with input from scientists and clinicians from King's College London and Massachusetts general hospital). Individuals with confirmed SARS-CoV-2 laboratory results, registering healthy on the app, with symptom duration of more than 7 days were included, considering the presentation at symptom peak to build the clustering.[15]

Multinomial regression modelling and time to admission - To quantify the relationship between demographic factors, co-morbidities and cluster membership we built a multinomial logistic regression model with the R package *nnet*. For binary variables, a missing value was assumed to correspond to the absence of a given co-morbidity. Individuals with missing values for age and sex were excluded from this analysis. The dependent variable was symptom cluster. The independent variables were; sex, age (categorical), chronic cardiac disease, chronic pulmonary disease, asthma, chronic kidney disease, chronic neurological disease, malignancy, chronic haematological disease, HIV, chronic rheumatological disease, dementia, malnutrition, chronic liver disease, and diabetes. Results are summarised as relative risk ratio (RRR) and 95% confidence intervals (95% CI). The average time from self-reported symptom onset to hospital admission in each cluster were compared using the Kruskal-Wallis test.

Survival analysis - To examine survival differences between symptom clusters we employed several methods. Kaplan-Meier curves for 30-day in-hospital mortality were calculated and compared using a log-rank test, with the R package *survival*. Individuals reported as being dead but with no outcome date were excluded. All individuals not reported as dead were presumed alive. Discharged individuals were retained within the at-risk set until the end of follow-up; thus, discharge did not compete death. Survival time was defined as the time in days between hospital admission and the reported outcome date. We then fitted a Cox proportional hazards model to the data with the *a priori* inclusion of age and sex as co-variates, using the R package *survival*. Given the non-linear effect of age on the risk of death we fitted age with a penalised smoothing spline. Results are reported as hazard ratio (HR) and 95% CI. In anticipation that the risk of death per cluster varied over time, we also calculated restricted mean survival times at 30 days, insuring the analysis against violations of proportional hazards assumptions. This was performed with the R package *survRM2*. Results are reported as mean survival difference (days) and 95% CI.

Results

For the initial cohort, 33468 patients were enrolled to the ISARIC-4C study, of which 7991 had fully missing symptom data and were excluded from our analysis (Supplementary Figure S1). The baseline characteristics of included patients (25477) are detailed in **Supplementary Table 1**. Overall, the median age was 73 (IQR 59-83) years and the majority of patients were male (15 046, 59%). On average, individuals presented to hospital 4 (IQR 1-8) days after the onset of symptoms.

Symptom prevalence and relationships

Cough was the most prevalent symptom (68% (95%CI 67.5-68.6%)), followed by fever (66.4% (95%CI 65.8-67%)), and dyspnoea (65.2% (95%CI 64.6-65.8%)) (**Figure 1a and Supplementary Table 2**). Furthermore, these were the only symptoms to be reported by greater than half of participants. The prevalence of individual symptoms varied with age (**Supplementary Figure S2**). Fever was less marked at the extremes of age, an observation which was also evident for dyspnoea, and, with the exception of those aged >90 years, for cough. Similarly, rash and runny nose were limited mostly to those aged <20 years, especially to those aged under 10 years. In sum, there were 4335 unique symptom combinations in the cohort, the most frequent being fever, cough, and dyspnoea (1430, 5.6%) (**Figure 1a**).

To explore the relationships between symptoms, we fitted an Ising model, employing L1-regularised logistic regression. The majority of symptoms exhibited some degree of conditional dependence with at least one other, however there were several that occurred independently; skin ulcers, rash, bleeding, lymphadenopathy, ear pain, and conjunctivitis (**Figure 1b**). All of which had a low prevalence (<5%). Uniquely, confusion was negatively associated with cough, myalgia, sore throat, and diarrhoea. Groupings of symptoms with interconnected, positive conditional dependencies were appreciable from inspection of the network graph. To formalise these structures, we used a short random walk algorithm. Excluding the 6 orphan symptoms, 6 distinct communities were identified (modularity=0.43). These include: core COVID-19 (fever, cough, and dyspnoea), upper

respiratory, bronchospasm, gastrointestinal (GI), neurological, and non-specific viral symptom sets (**Figure 1b**).

Patient clusters by symptom pattern

To identify symptom groupings within the study cohort, we performed unsupervised partitional clustering. An *a priori* assessment suggested that 7 clusters were optimal. This combined the inflection points in the decline in total sum of squares and the rise in gap statistic, with the nearest peak in average silhouette width (**Supplementary Figure S3**).

The patterns of symptoms within the seven clusters are shown in **Figure 2a**. Based on the cluster medoid case, we characterised them as: core COVID-19 symptoms (fever, cough, and dyspnoea); core symptoms plus fatigue and confusion; productive cough; gastrointestinal (GI) symptoms; pauci-symptomatic; afebrile; and confusion. The core symptoms cluster accounted for the largest number of patients (9364, 36.8%) and the GI symptoms cluster the fewest (1327, 5.2%). Measures of cluster internal validity and stability are presented in **Supplementary Figure S4a**.

To examine the implications of our handling of missing data, we performed a sensitivity analysis by clustering only cases with fully complete symptom data (12712, 49.9%). This analysis retained the cluster structure, with the exception of the afebrile cluster, in which the medoid case exhibited dyspnoea alone (**Supplementary Figure S4b**). The simple agreement between iterations was 89.2%, with a Cohen's kappa of 0.86 ($p < 0.001$).

To validate the clusters identified by our primary analysis, we undertook two validation steps. First, we repeated our clustering approach on a cohort of patients enrolled to the ISARIC CCP-UK after those in the primary analysis and up until 7th July, 2020 (n=35446). Of these, 1912 (5.4%) had fully incomplete symptom data and were excluded from analysis. Clustering returned identical cluster medoids, with the exception of the afebrile cluster, in which cough was no longer implicated (**Supplementary Figure S5**). This cluster was also reduced in relative size (14.2% to 6.7%).

Secondly, our clustering approach was replicated in an outpatient cohort (COVID Symptom Study, n=4445). This study records several overlapping or closely associated symptoms. Despite differences in study design and population, similar symptom groupings are discernible, including GI (cluster 1), pauci-symptomatic (cluster 2), and confusion clusters (cluster 5) (**Supplementary Figure S6**).

Association of patient characteristics with symptom cluster

Compared to the cohort average, those in the GI symptoms cluster were younger (60 years (49-72)), while those with core symptoms, fatigue and confusion (79 years (70-85)) or confusion alone (82 years (75-88)), were older (**Figure 2b**). The GI symptom cluster also had the highest proportion of female patients (628, 47%). These differences were accompanied by variations in the median time from symptom onset to hospital admission between symptom clusters ($p < 0.001$) (**Figure 3a**), and similarly, in the burden of co-morbidity (**Figure 3b**).

To quantify these differences, we used a multinomial logistic regression model. Taking the largest cluster (core symptoms) as our reference, we included major demographic variables and co-morbidities in the analysis (**Figure 3c and Supplementary Table S3**). By comparison, those in the GI symptoms (RRR 0.66, 95% CI 0.60 to 0.73, p<0.001), afebrile (RRR 0.84, 95%CI 0.76 to 0.92, p<0.001), confusion (RRR 0.79, 95%CI 0.70 to 0.90, p<0.001), and pauci-symptomatic (RRR 0.78, 95%CI 0.72 to 0.86, p<0.001) clusters, were more likely to be female (**Figure 3c**). The association between advanced age and confusion was mirrored by a higher prevalence of dementia in these groups (**Figure 3c and Supplementary Figure S3a**). Patients assigned to the productive cough cluster were more likely to suffer from chronic pulmonary diseases (RRR 2.07, 95%CI 1.84 to 2.33, p<0.001) and asthma (RRR 1.56, 95% CI 1.37 to 1.77, p<0.001) (**Figure 3c**).

Association between symptom cluster and outcome

Overall, the unadjusted in-hospital mortality was 35%, with 24% having an incomplete hospital episode at the end of follow-up. Outcomes, stratified by cluster allocation, are detailed in **Supplementary Table S1**. To assess differences in mortality between symptom clusters, we first compared Kaplan-Meier curves (log-rank test, p<0.001) (**Figure 4a**). For the largest cluster, core symptoms, unadjusted in-hospital mortality was 33%. The lowest mortality was found in the GI symptoms cluster (18%) and the highest in the core, fatigue, and confusion cluster (53%). Subsequently, we used a Cox proportional hazards model to account for the influence of age and sex (**Figure 3b**). Those in the core, fatigue, and confusion cluster remained at the highest risk of death when compared to those with core symptoms, (HR 1.26, 95%CI 1.15-1.37, p <0.001). However, membership of the confusion

cluster was no longer associated with an increased risk of death (HR 0.92, 95%CI 0.83-1.02, p=0.096). Those in the productive cough, GI, and pauci-symptomatic clusters continued to attract a lower risk of death (**Figure 4b**). Given that there was evidence of variation in risk over time for some clusters, we performed Restricted Mean Survival Time (RMST) analyses (**Supplementary Table S4**). By this method, males in the core, fatigue, and confusion cluster had the poorest survival compared to core symptoms, mean survival difference at 30-days -1.9 days (95% CI -2.8 - 1.1).

Discussion

This study identifies distinct symptom clusters in a large cohort of hospitalised patients with COVID-19. These clusters are internally robust and reproducible. To our knowledge, this report also provides the largest dataset of symptom prevalence in COVID-19 patients to date.

Knowledge of distinct symptom sub-phenotypes has potential importance for our mechanistic understanding of COVID-19. Two groups in our analysis have distinct clinical trajectories: those presenting with GI symptoms, and those presenting with confusion. Those in the GI cluster tended to be younger, more likely female, presented to hospital later, and had a higher probability of survival. Conversely, those with confusion (with or without fever, cough, and dyspnoea), were older, presented earlier, and had poorer outcomes. These data may be important for refining risk-prediction at the time of hospital admission. Similarly, the identification of a cluster in which patients had few symptoms other than confusion has implications for defining cases and for targeting testing,

particularly in elderly patients. We suggest that patients presenting with isolated diarrhoea, vomiting, abdominal pain, or new confusion of unknown aetiology should be tested for COVID-19. Importantly, these clusters have divergent outcomes from those with core COVID-19 symptoms.

Gastrointestinal infection occurred in SARS,[16] MERS,[17] and was reported in early descriptions of COVID-19.[18] Single-cell transcriptomic analysis from ileum and colon has demonstrated the ability of SARS-CoV-2 to infect enterocytes,[19] leading to the possibility of an enteric form of COVID-19.[20]

Our identification of a group of COVID-19 patients presenting with confusion, and not other symptoms, has direct clinical implications. The causal mechanisms leading to this presentation may not be directly related to COVID-19: confusion is a common nonspecific presenting symptom, particularly among elderly patients. However, emerging evidence suggests that SARS-CoV-2 may enter the CNS directly via the olfactory bulb, and precipitates inflammation with direct effects on the brain.[21] Importantly, this group are at higher absolute risk of death.

These data may offer a starting point for predictive enrichment in clinical trials.[22] Predictive enrichment based on symptom clustering is expected to perform best where causal relationships exist between fundamental biological or genomic features of disease and the clinical manifestations of severe illness.[23] Similar relationships have been described in conditions as diverse as schizophrenia[24] and asthma.[25] The re-analysis of trial results based on patient clustering may reveal differential treatment effects.[26]

The pooled symptom prevalences reported in the largest meta-analysis of independent studies (including 24401 individuals), as well as those found in the WHO-China Joint Mission Report, are broadly consistent with ours, taking into account the higher severity of illness and more advanced age in our cohort.[27,28] However, the prevalence of GI symptoms and of confusion was higher in our study.

This study has some limitations. First, symptoms were sought only at hospital admission, potentially disposing patients to recall bias given the time between symptom onset and presentation. Similarly, patients may have elected to describe symptoms at that time or the gamut of symptoms since the onset of illness. Additionally, a small number of symptoms now known to be associated with COVID-19, namely anosmia and ageusia,[29] were not recorded. Therefore, these data may not be generalisable to individuals with milder disease who do not require admission to hospital. Second, our study had missing data. In handling missing symptom records, we sought to retain as much data as possible given its informative missingness. This approach was robust to a sensitivity analysis. For survival data this was more challenging, and several methods of analysis were employed to reduce the risk of bias.

A limitation of partitional clustering is the need to pre-specify the number of clusters. In a large, heterogeneous population, this requires investigators to strike a balance between parsimony and granularity. Each patient is unique, and there were 4335 symptom combinations in our cohort; hence, the most granular clustering would reveal 4335 distinct patterns of disease. Our purpose in grouping these patients is to reveal clinical patterns that

will have practical utility. As we have argued previously, the question should not be "How many clusters exist?", but rather, "Which clusters are potentially useful?".[23]

Finally, statistical modelling in this study corrected for a limited number of co-variates. With respect to differences in patient characteristics and symptom cluster, it may be that unmodelled demographic or clinical variables account partially or wholly for the variations which we observed. Likewise, for survival analysis, we adjusted only for age and sex, both of which we know to have been largely complete and not subject to significant confounding. Additionally, for some clusters there was evidence of variation in risk of death with time. This violates the assumption of proportional hazards and may limit the interpretation of the log-rank test and hazard ratios. We attempted to defend against this violation by performing RMST analyses, which confirmed the directions of effect.

In summary, our study of 68914 hospitalised patients with COVID-19 identified distinct symptom sub-groupings whose character and outcome differed significantly from those with the core symptoms of COVID-19. These observations deepen our understanding of COVID-19 and will influence clinical diagnosis, risk prediction, and future mechanistic and clinical studies.

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Figure Legends

Figure 1. Symptom prevalence and relationships. a. Symptom prevalence. Upset plot, intersections describe the 'top 10' symptom combinations within the cohort. The upper graph charts the total number of patients exhibiting these symptom sets. The lower graph charts the total number of patients with each symptom in the cohort. **b.** Symptom network graph derived using eLasso. Lines between symptom nodes illustrate conditional dependencies. A thicker line width and darker hue represents a stronger positive conditional dependence. Red lines represent a negative conditional dependence.

Figure 2. Symptom clusters. a. Cluster identities, proportions, and patterns. Data are presented as the percentage of patients reporting symptom within each cluster. **b.** Distribution of age by symptom cluster. Density plots, solid lines represent the median age.

Figure 3. Patient characteristics and symptom clusters. a. Time from symptom onset to hospital admission. Data are presented as counts in single day bins. Vertical dashed lines represent the median time (days). **b.** Co-morbidities by symptom cluster. Percentage of individuals with co-morbidity at time of admission. **c.** Association between patient characteristics and symptom cluster membership. Multinomial regression, data are presented as relative risk ratio (95% confidence interval). Core symptoms chosen as reference cluster. The age group 60-80 years serves as the reference group for age and includes the median age for the cohort.

Figure 4. Symptom clusters and survival. a. Unadjusted 30-day in-hospital mortality by cluster. Kaplan-Meier curves, those discharged before 30 days were assumed to have survived until the end of follow-up. **b.** The risk of 30 day in-hospital mortality, adjusted for age and sex. Upper panel - Forest plot, showing results of a Cox proportional hazards model. Lower panel - hazard ratio associated with varying age, fitted with penalized B splines. Data are presented as hazard ratio (HR) and 95% confidence intervals. Red dotted lines represent the 95% Cis. Core symptoms serves as the reference symptom cluster. The cohort median age serves as the reference age.

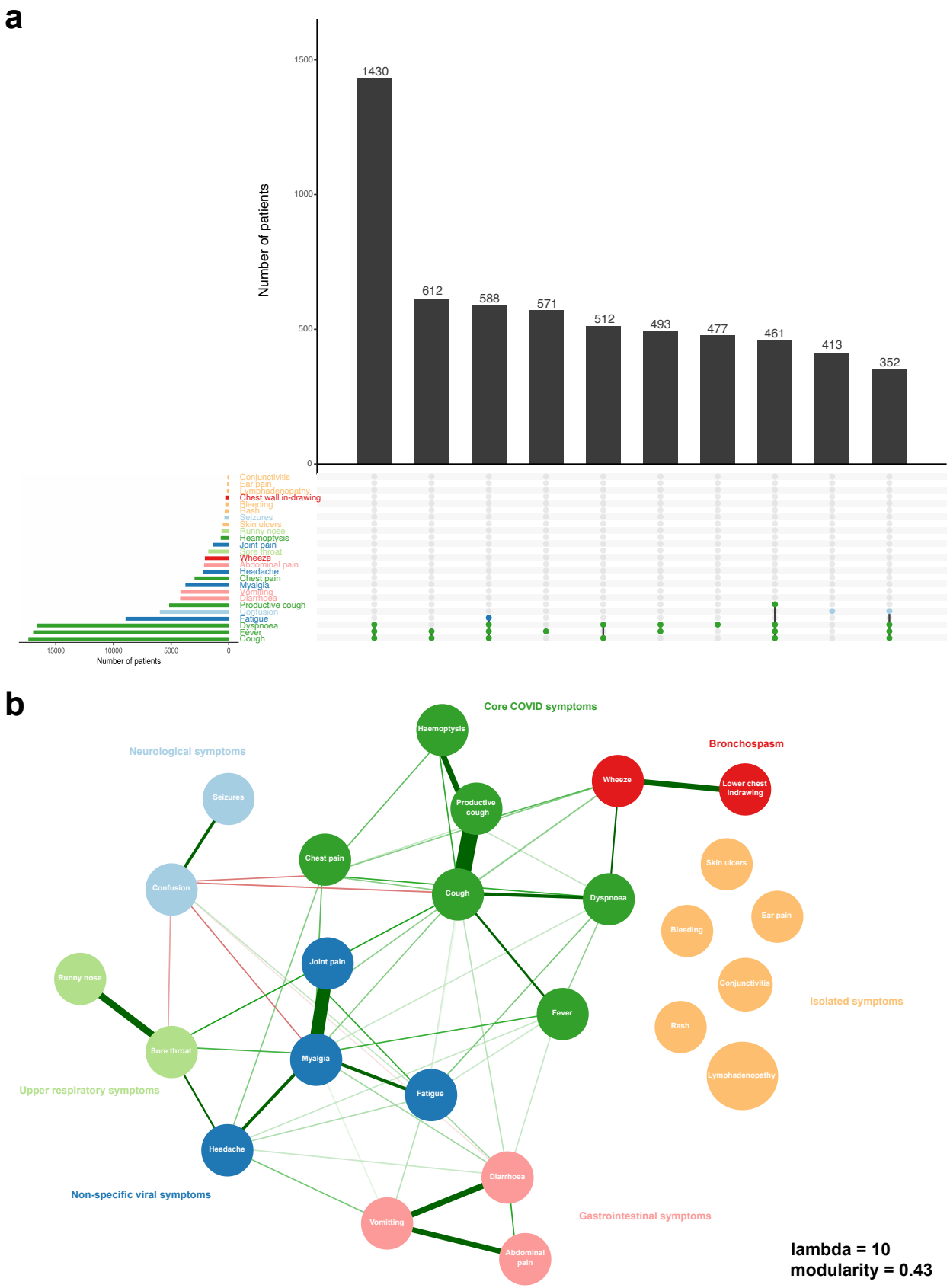


Figure 1. Symptom prevalence and relationships.

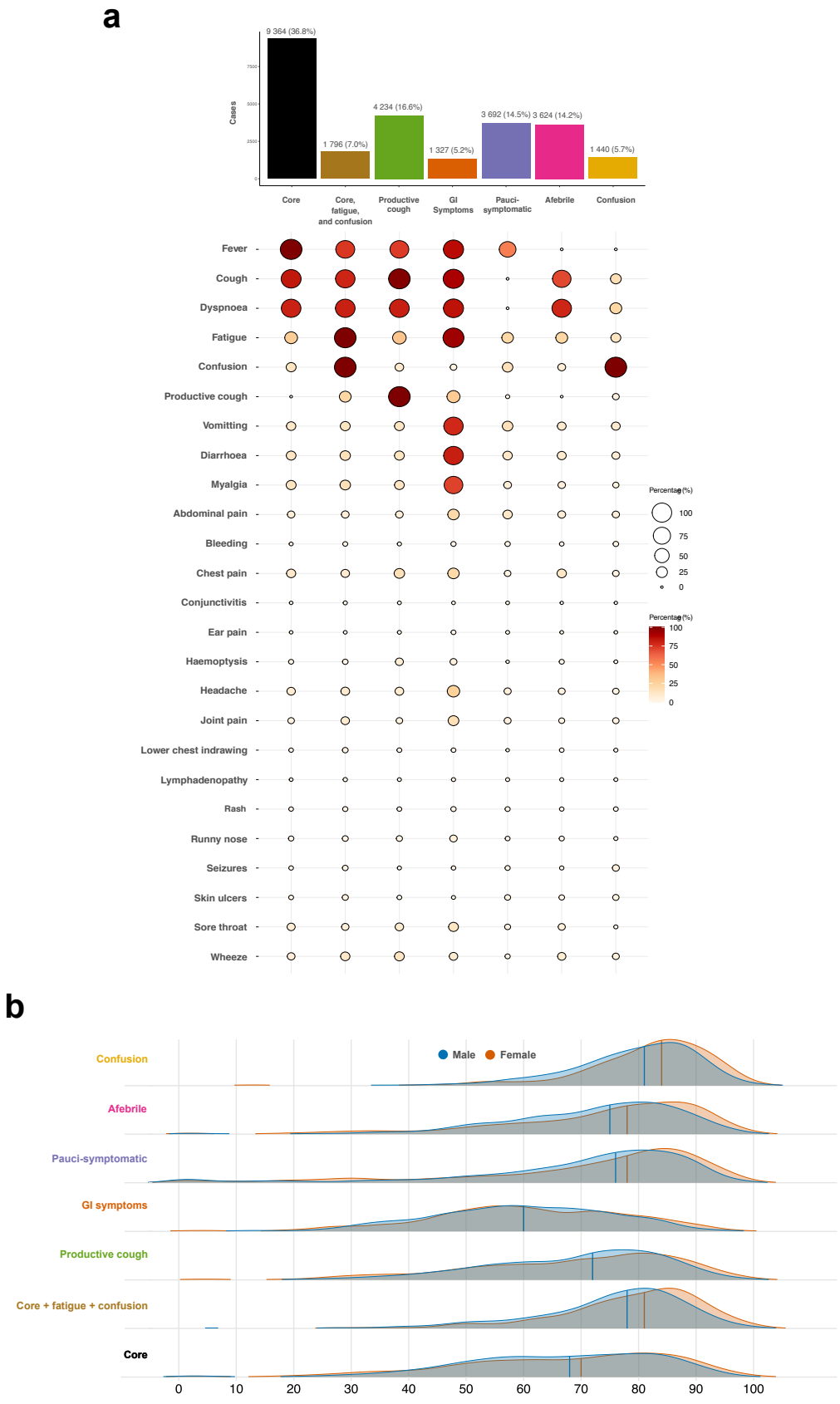


Figure 2. Symptom clusters.

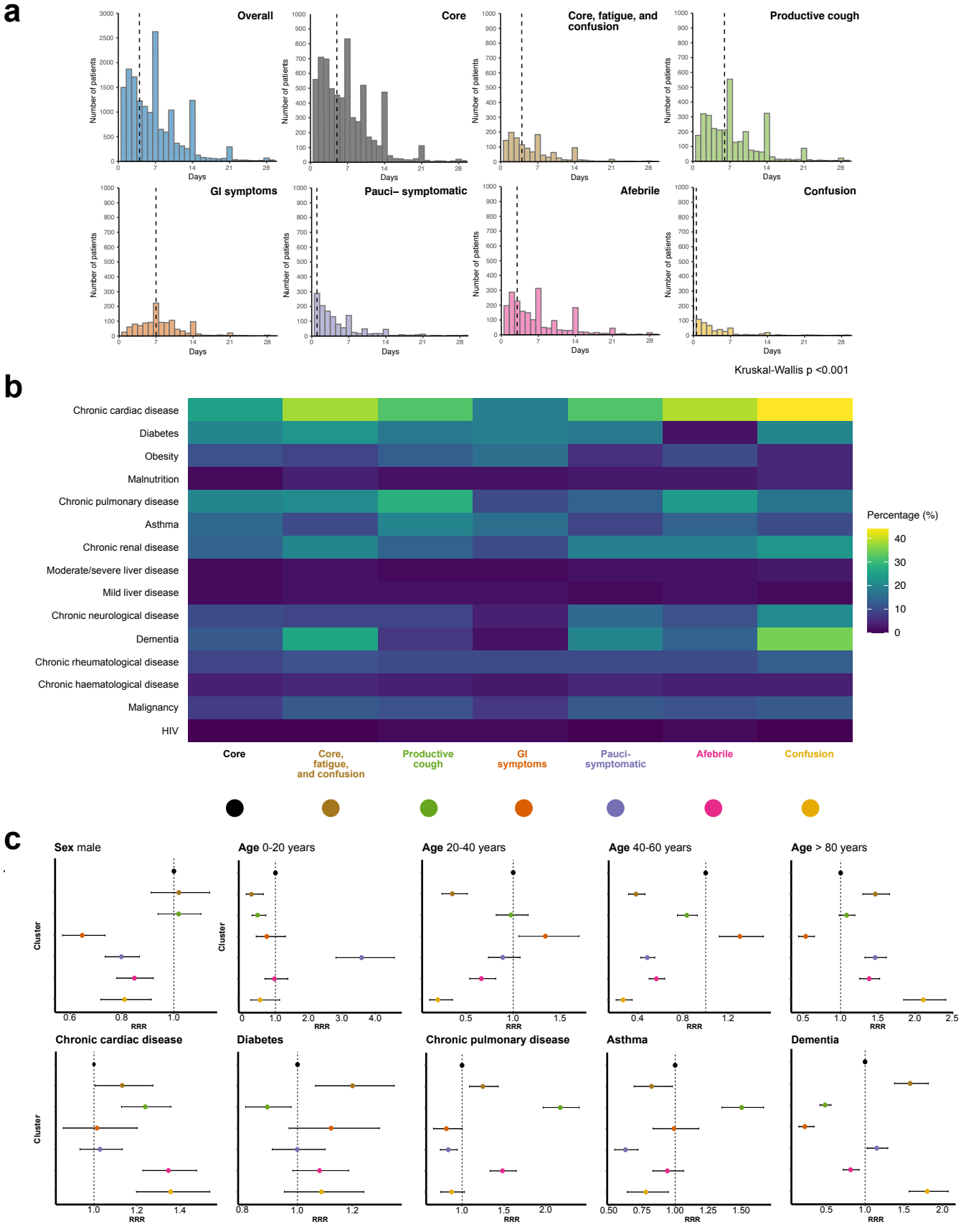


Figure 3. Patient characteristics and symptom clusters.

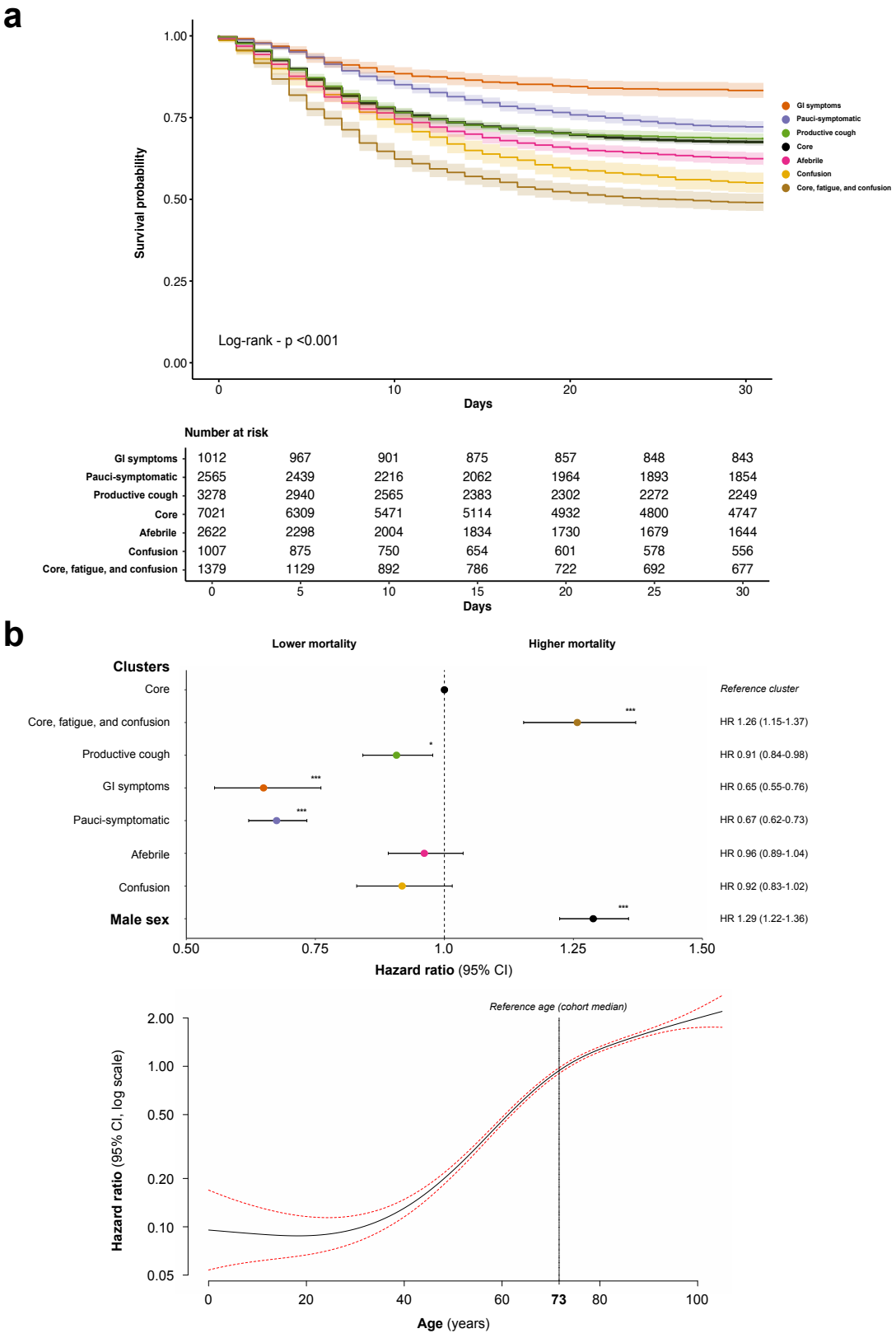


Figure 4. Symptom clusters and survival.

Supplement

Supplementary Figure Legends

Supplementary Figure S1. Missing symptom data. a. Summary of missing symptom data by case. **b.** Patterns of missing symptom data. Upset plot, intersections represent the 'top 10' missing symptom combinations. Upper graph – summarises the number of patients with each pattern. Lower graph – the total number of patients with missing data for each symptom.

Supplementary Figure S2. Symptom proportions and patterns by age. Data are presented as the percentage of patients reporting each symptom within each decile.

Supplementary Figure S3. Measures of optimal cluster number. a. total within sum of squares. **b.** Average silhouette width. **c.** Gap statistic. Data are presented across a range of *k* (1-10). Dashed vertical lines represent the selected cluster number.

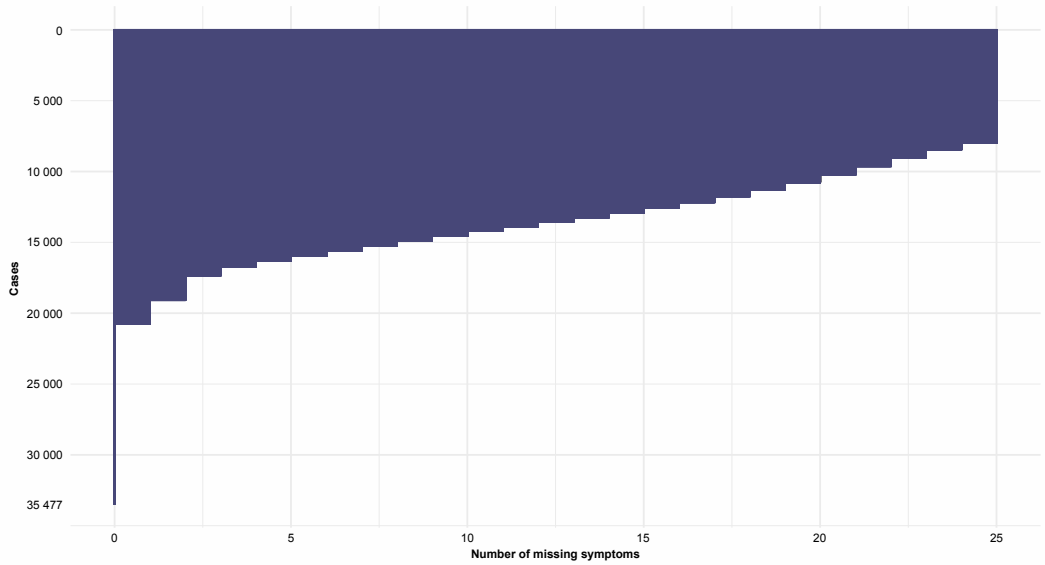
Supplementary Figure S4. Cluster internal validity and sensitivity analysis. a. Measures of clustering internal validity and stability for *k* = 7. * Average dissimilarity – average dissimilarity between observations in the cluster and the cluster medoid. † Isolation – maximal dissimilarity between observations in the cluster and the cluster medoid divided by minimal dissimilarity between the cluster medoid and the medoid of any other cluster (a smaller ratio indicates a more isolated cluster). ‡ Jaccard bootstrap – the cluster-wise Jaccard coefficient for 1000 iterations of the clustering algorithm on random subsets of the

data. **b.** Sensitivity analysis. Clusters and patterns of symptoms in patients with fully complete symptom data (n=12712). Data are presented as the percentage of patients reporting symptom within each cluster.

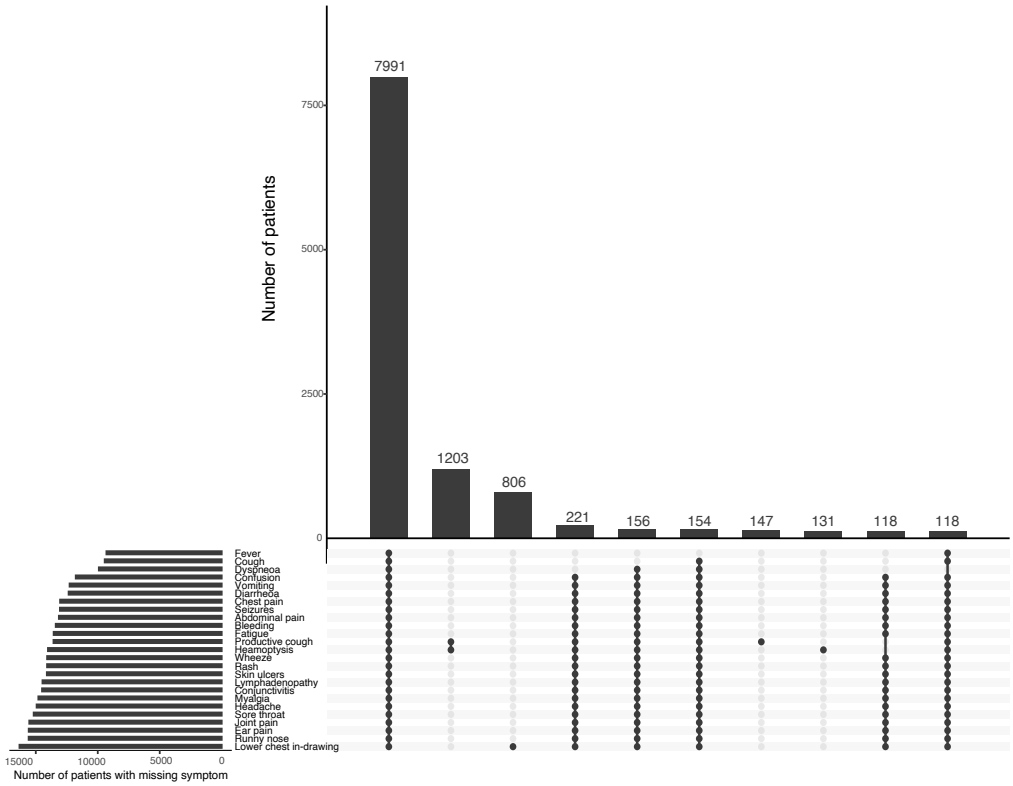
Supplementary Figure S5. Internal clustering validation. Clusters, proportions and patterns, in an analysis of patients enrolled to the CCP-UK after the primary analysis, up to 7th July, 2020 (n=33534). Data are presented as the percentage of patients reporting symptom within each cluster.

Supplementary Figure S6. External clustering validation. Clusters and patterns of symptoms in a cohort of patients enrolled in the COVID Symptom Study. Data are presented as the percentage of patients reporting symptom within each cluster.

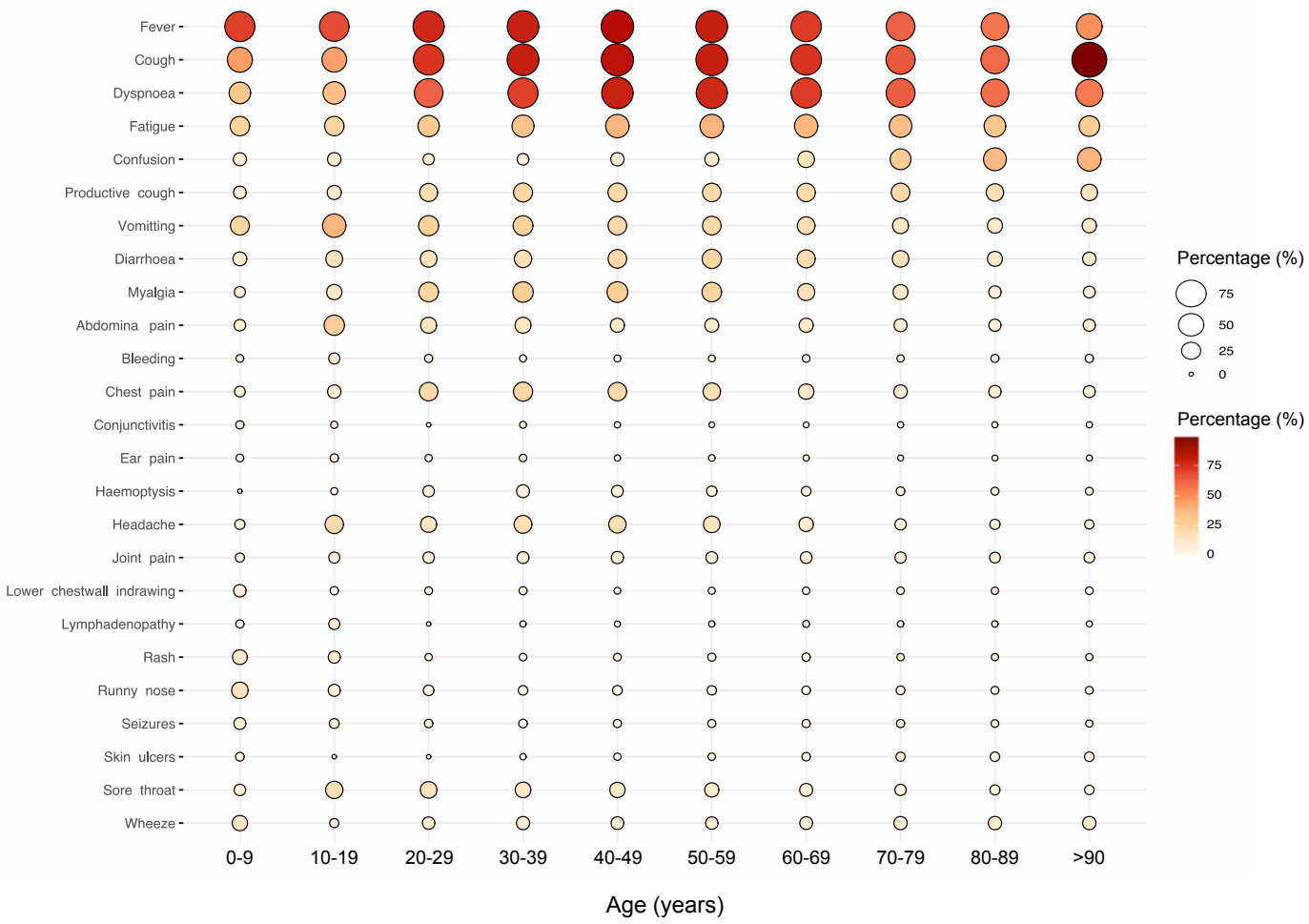
a



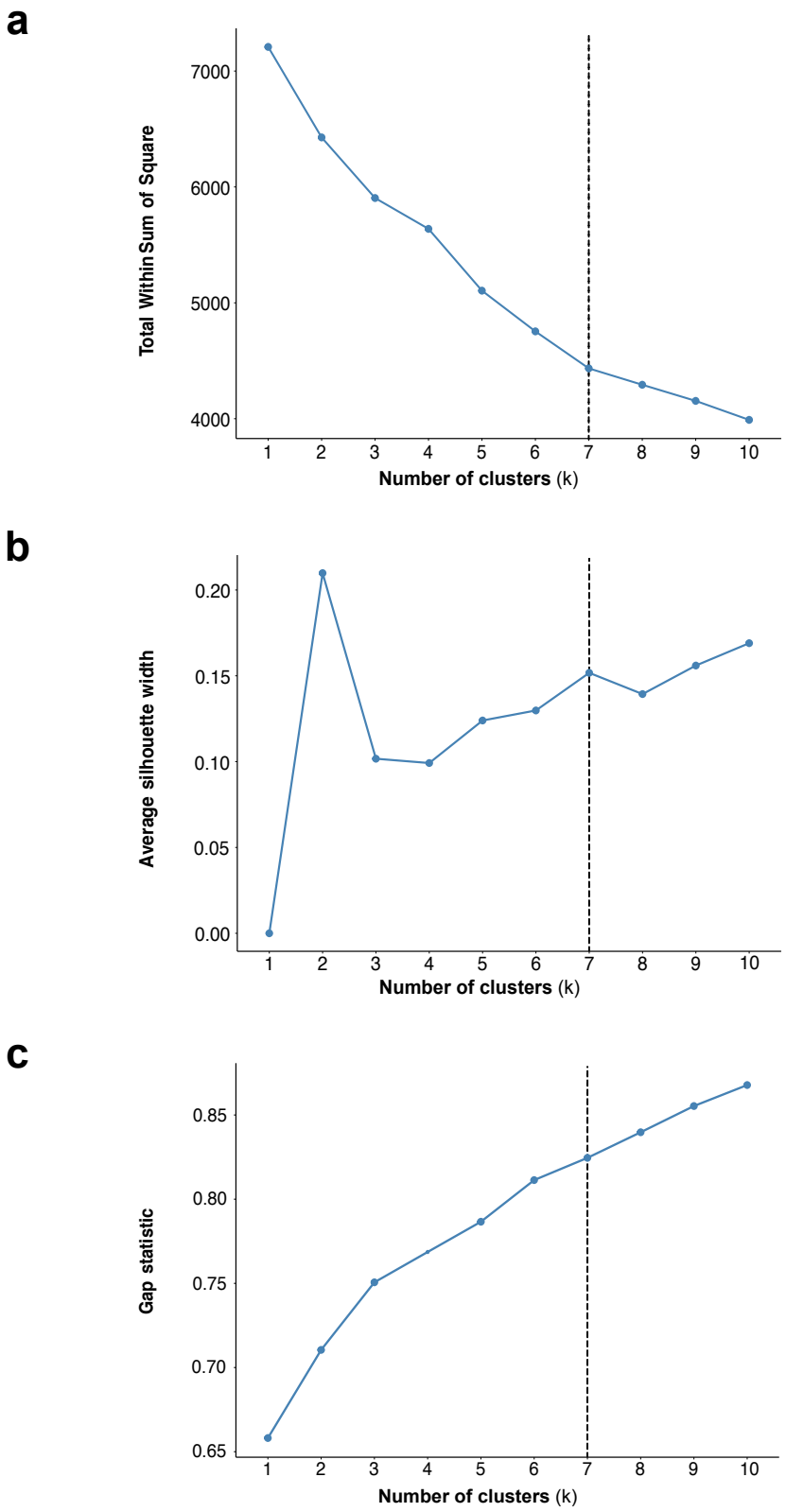
b



Supplementary Figure S1. Missing symptom data.



Supplementary Figure S2. Symptom proportions and patterns by age.

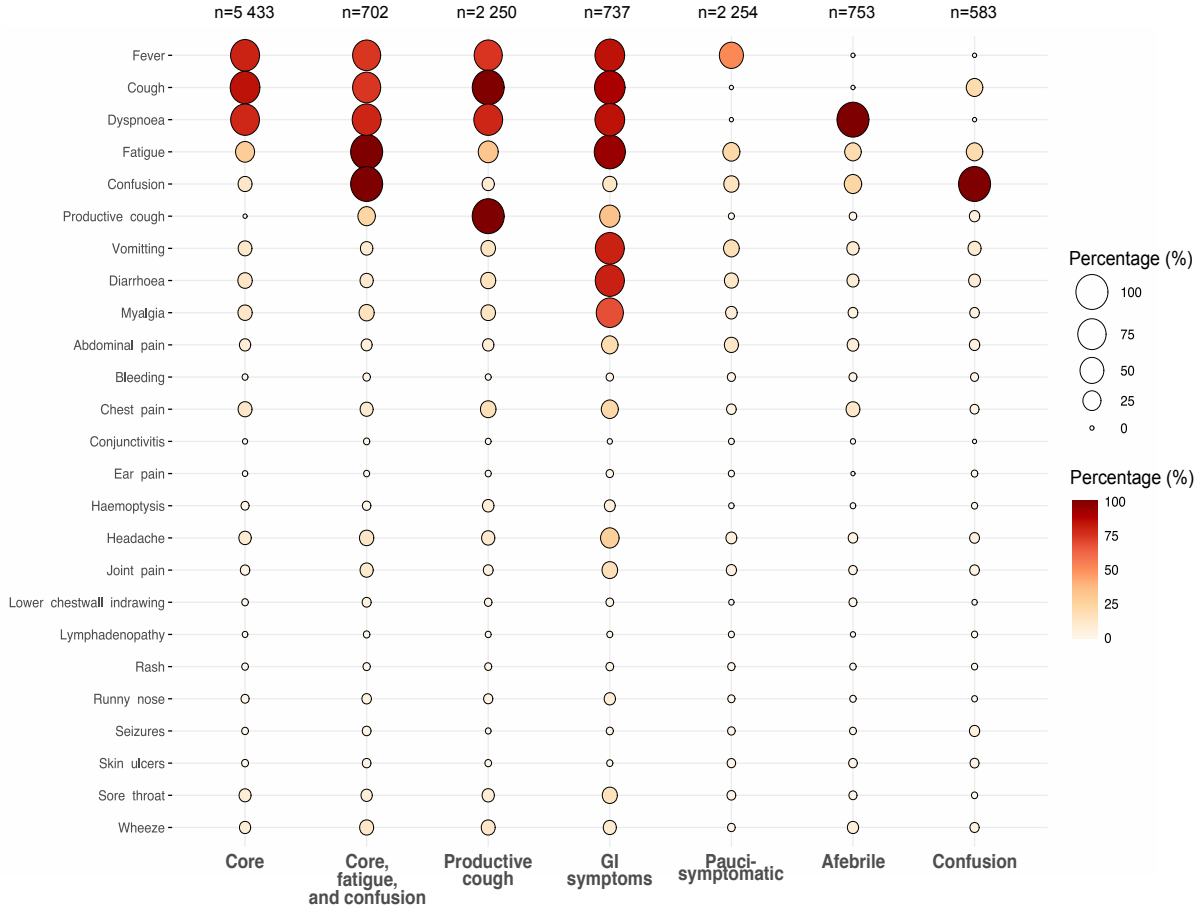


Supplementary Figure S3. Measures of optimal cluster number.

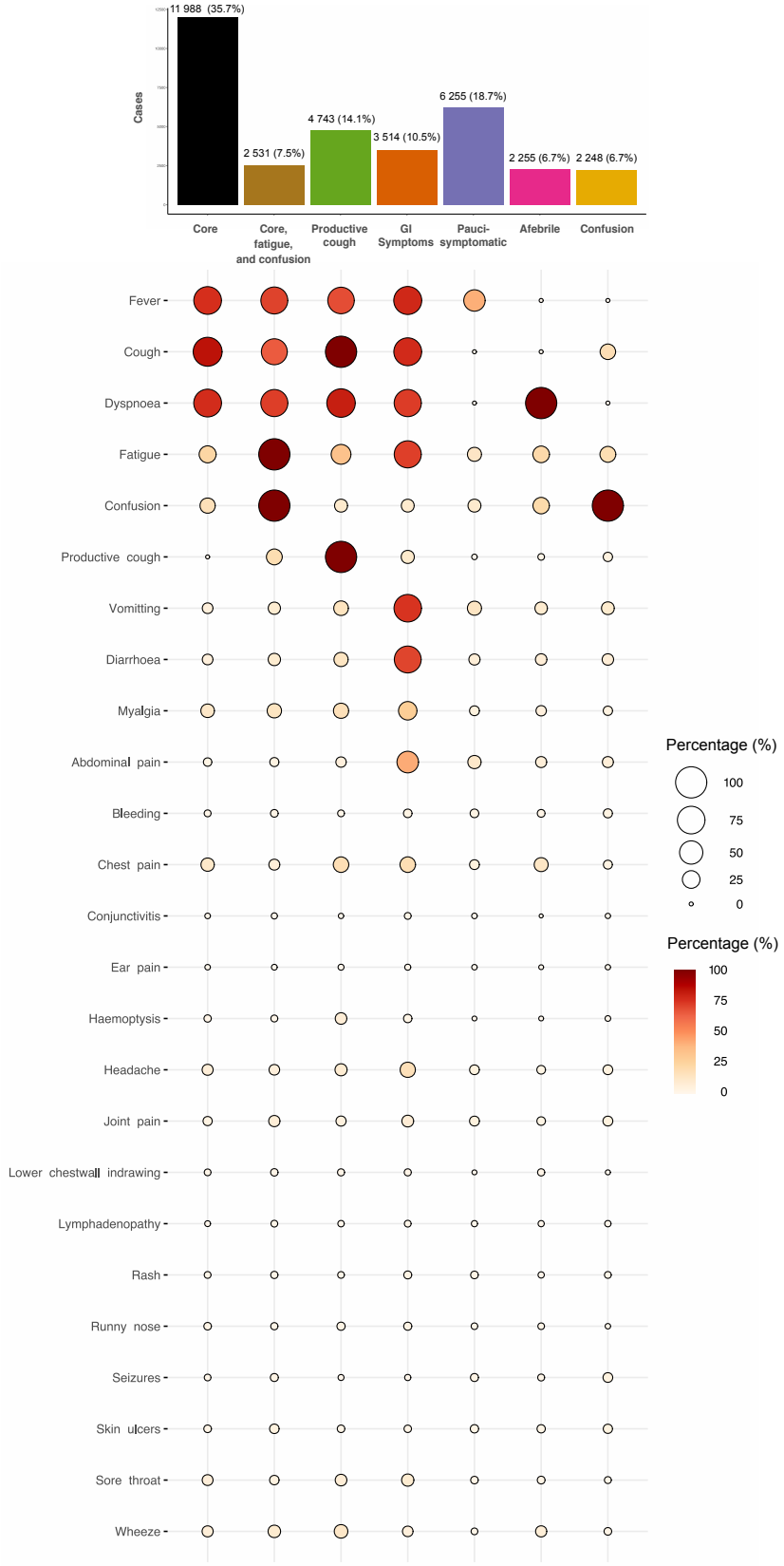
a

Cluster	Average dissimilarity*	Isolation†	Jaccard bootstrap‡
Core	0.26	3.00	0.62
Core +fatigue +Confusion	0.37	2.19	0.58
Productive cough	0.32	3.50	0.68
GI symptoms	0.55	2.00	0.67
Pauci–symptomatic	0.34	1.13	0.53
Cough and dyspnea	0.40	2.50	0.71
Confusion	0.37	1.04	0.61

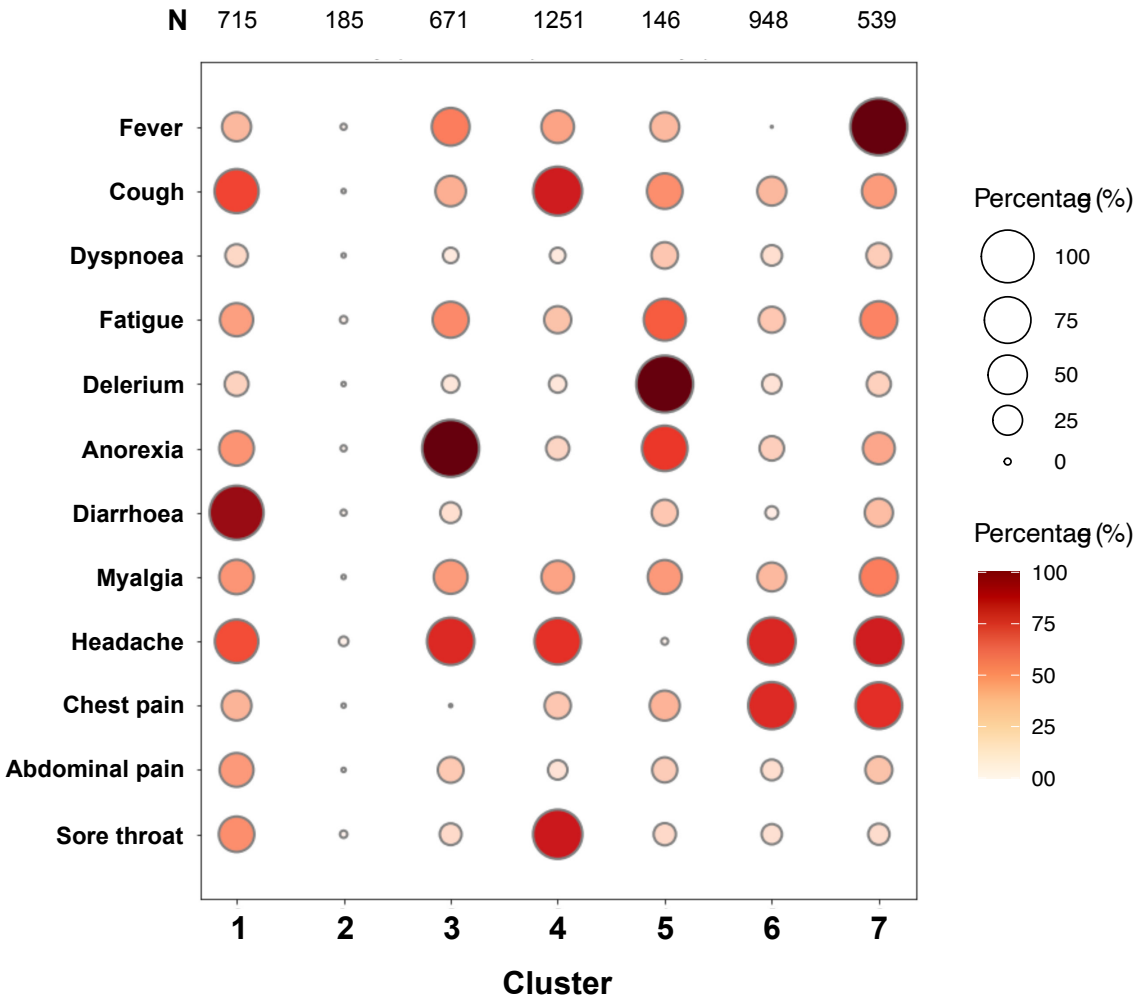
b



Supplementary Figure S4. Cluster internal validity and sensitivity analysis.



Supplementary Figure S5. Internal clustering validation.



Supplementary Figure S6. External clustering validation.

Supplementary Tables

Supplementary Table 1. Patient characteristics and outcomes.

	N	Core n = 9364	Core, fatigue, and confusion n = 1796	Productive cough n = 4234	GI symptoms n = 1327	Pauci-symptomatic n = 3692	Afebrile n = 3624	Confusion n = 1440	Overall n = 25477
Age	23493	68 (55, 82)	69 (55, 81)	72 (58, 81)	60 (49, 72)	76 (63, 85)	76 (64, 85)	82 (75, 88)	73 (59, 83)
Sex (male)	25359	5735 (61%)	1106 (62%)	2600 (62%)	699 (53%)	2033 (55%)	2084 (58%)	789 (55%)	15,046 (59%)
Ethnicity	22643								
Aboriginal/First Nations		2 (<0.1%)	0 (0%)	1 (<0.1%)	0 (0%)	1 (<0.1%)	2 (<0.1%)	1 (<0.1%)	7 (<0.1%)
Arab		55 (1%)	6 (<1%)	19 (1%)	4 (<1%)	14 (<1%)	16 (1%)	3 (<1%)	117 (1%)
Black		351 (4%)	46 (3%)	163 (4%)	40 (3%)	119 (4%)	87 (3%)	31 (2%)	837 (4%)
East Asian		100 (1%)	16 (1%)	24 (1%)	13 (1%)	29 (1%)	23 (1%)	6 (1%)	211 (1%)
South Asian		412 (5%)	50 (3%)	167 (4%)	71 (6%)	102 (3%)	116 (4%)	18 (1%)	936 (4%)
West Asian		36 (<1%)	3 (<1%)	14 (<1%)	5 (<1%)	11 (<1%)	12 (<1%)	7 (1%)	88 (<1%)
Latin American		17 (<1%)	1 (<0.1%)	9 (<1%)	2 (<1%)	7 (<1%)	5 (<1%)	1 (<0.1%)	42 (<1%)
White		6592 (80%)	1441 (81%)	3100 (82%)	960 (81%)	2807 (85%)	2578 (86%)	1166 (91%)	18,824 (83%)
Other		687 (8%)	94 (6%)	266 (7%)	91 (8%)	194 (6%)	194 (6%)	55 (4%)	1581 (7%)
Co-morbidities									
Chronic cardiac disease	23933	2243 (25%)	648 (38%)	1289 (32%)	244 (19%)	1090 (32%)	1302 (39%)	602 (44%)	7418 (31%)
Diabetes	23670	1701 (20%)	395 (23%)	724 (18%)	238 (19%)	625 (18%)	723 (22%)	266 (20%)	4672 (20%)
Obesity	21707	913 (11%)	146 (9%)	480 (13%)	193 (16%)	200 (6%)	291 (10%)	65 (5%)	2288 (11%)
Malnutrition	22511	119 (1%)	69 (4%)	67 (2%)	21 (2%)	105 (3%)	79 (3%)	66 (5%)	526 (2%)
Chronic pulmonary disease, not asthma	23828	1229 (14%)	351 (21%)	1118 (28%)	128 (10%)	477 (14%)	780 (24%)	223 (17%)	4306 (18%)
Asthma	23732	1279 (15%)	177 (10%)	812 (20%)	205 (16%)	297 (9%)	444 (14%)	129 (10%)	3343 (14%)
Chronic renal disease	23685	1238 (14%)	342 (20%)	571 (14%)	126 (10%)	653 (19%)	610 (19%)	310 (23%)	3850 (16%)
Moderate/severe liver disease	23481	120 (1%)	41 (2%)	57 (1%)	18 (1%)	69 (2%)	69 (2%)	41 (3%)	415 (2%)
Mild liver disease	23431	107 (1%)	39 (2%)	73 (2%)	25 (2%)	41 (1%)	59 (2%)	16 (1%)	360 (2%)
Chronic neurological disease	23530	862 (10%)	327 (9%)	340 (9%)	55 (4%)	504 (15%)	355 (11%)	278 (21%)	2721 (12%)
Dementia	23630	1050 (12%)	447 (26%)	271 (7%)	23 (2%)	650 (20%)	466 (14%)	467 (35%)	3374 (14%)
Chronic rheumatological disease	23407	783 (9%)	182 (11%)	403 (10%)	123 (10%)	347 (10%)	332 (10%)	167 (13%)	2337 (10%)
Chronic haematological disease	23454	340 (4.0%)	76 (5%)	169 (4%)	35 (3%)	163 (5%)	129 (4%)	52 (4%)	964 (4%)
Malignancy	23487	701 (8%)	196 (12%)	422 (11%)	90 (7%)	410 (12%)	343 (11%)	158 (12%)	2320 (10%)
HIV	23311	37 (<1%)	7 (<1%)	22 (1%)	10 (1%)	10 (<1%)	15 (1%)	3 (<1%)	104 (%)
Smoking status	18357								
Former Smoker		1935 (29%)	469 (36%)	1232 (37%)	345 (32%)	690 (28%)	859 (34%)	308 (33%)	5838 (32%)
Never Smoked		4396 (66%)	735 (57%)	1879 (56%)	702 (64%)	1603 (64%)	1432 (58%)	556 (60%)	11,321 (62%)
Yes		362 (5%)	85 (7%)	235 (7%)	44 (4%)	207 (8%)	195 (8%)	70 (8%)	1198 (6.5%)
Outcomes									
ICU admission	24443	1841 (21%)	224 (13%)	700 (17%)	293 (23%)	266 (7.5%)	453 (13%)	69 (5.0%)	3846 (16%)
Mechanical ventilation	23907	1073 (12%)	468 (13%)	137 (8%)	153 (12%)	130 (4%)	268 (8%)	35 (3%)	2174 (9%)
Mortality	19358	2402 (33%)	741 (53%)	1104 (33%)	186 (18%)	830 (31%)	1086 (40%)	502 (48%)	6851 (35%)
Unknown Mortality	6119	2191 (23%)	389 (22%)	889 (21%)	297 (22%)	1029 (28%)	920 (25%)	404 (28%)	6119 (24%)

Supplementary Table 2. Symptom prevalence

Symptom	**Number of patients** (n=25 477)	**Prevalence** (95% CI)
Cough	17 334	68.0 (67.5-68.6)
Fever	16 920	66.4 (65.8-67.0)
Dyspnoea	16 603	65.2 (64.6-65.8)
Fatigue	8 906	35.0 (34.4-35.5)
Confusion	5 935	23.3 (22.8-23.8)
Productive cough	5 125	20.1 (19.6-20.6)
Diarrhoea	4 171	16.4 (15.9-16.8)
Vomiting	4 144	16.3 (15.8-16.7)
Myalgia	3 719	14.6 (14.2-15.0)
Chest pain	2 925	11.5 (11.1-11.9)
Headache	2 213	8.7 (8.3-9.0)
Abdominal pain	2 094	8.2 (7.9-8.6)
Wheeze	2 029	8.0 (7.6-8.3)
Sore throat	1 731	6.8 (6.5-7.1)
Joint pain	1 294	5.1 (4.8-5.4)
Haemoptysis	652	2.6 (2.4-2.8)
Runny nose	583	2.3 (2.1-2.5)
Skin ulcers	473	1.9 (1.7-2.0)
Seizures	336	1.3 (1.2-1.5)
Rash	307	1.2 (1.1-1.3)
Bleeding	259	1.0 (0.9-1.1)
Chest wall in-drawing	254	1.0 (0.9-1.1)
Lymphadenopathy	119	0.5 (0.4-0.6)
Ear pain	98	0.4 (0.3-0.5)
Conjunctivitis	73	0.3 (0.2-0.4)

Supplementary Table 3. Multinomial regression relative risk ratios.

	Cluster	Odds ratio (OR)	95% CI	P value
Male sex	Core		*reference*	
	Core, fatigue, and cough	1.02	0.91-1.14	0.743
	Productive cough	1.02	0.94-1.10	0.660
	GI symptoms	0.65	0.57-0.73	<0.001
	Pauci-symptomatic	0.80	0.73-0.87	<0.001
	Afebrile	0.85	0.78-0.92	<0.001
	Confusion	0.81	0.72-0.91	<0.001
Age 0-20	Core		*reference*	
	Core, fatigue, and cough	0.28	0.12-0.64	0.002
	Productive cough	0.46	0.30-0.72	<0.001
	GI symptoms	0.74	0.42-1.30	0.295
	Pauci-symptomatic	3.59	2.81-4.57	<0.001
	Afebrile	0.97	0.68-1.37	0.863
	Confusion	0.55	0.26-1.13	0.101
Age 20-40	Core		*reference*	
	Core, fatigue, and cough	0.35	0.24-0.51	<0.001
	Productive cough	0.97	0.82-1.16	0.771
	GI symptoms	1.34	1.06-1.70	0.014
	Pauci-symptomatic	0.89	0.74-1.07	0.221
	Afebrile	0.66	0.54-0.81	<0.001
	Confusion	0.20	0.11-0.36	<0.001
Age 40-60	Core		*reference*	
	Core, fatigue, and cough	0.38	0.32-0.46	<0.001
	Productive cough	0.83	0.75-0.93	<0.001
	GI symptoms	1.30	1.12.-1.51	<0.001
	Pauci-symptomatic	0.48	0.42-0.55	<0.001
	Afebrile	0.56	0.50-0.64	<0.001
	Confusion	0.27	0.21-0.35	<0.001
Age >80	Core		*reference*	
	Core, fatigue, and cough	1.46	1.30-1.66	<0.001
	Productive cough	1.08	0.98-1.19	0.123
	GI symptoms	0.53	0.44-0.65	<0.001
	Pauci-symptomatic	1.46	1.33-1.61	<0.001
	Afebrile	1.38	1.26-1.52	<0.001
	Confusion	2.11	1.85-2.41	<0.001

	Cluster	Odds ratio (OR)	95% CI	P value
Chronic cardiac disease	Core		*reference*	
	Core, fatigue, and cough	1.13	1.00-1.27	0.041
	Productive cough	1.24	1.13-1.36	<0.001
	GI symptoms	1.01	0.86-1.20	0.868
	Pauci-symptomatic	1.03	.93-1.13	0.569
	Afebrile	1.35	1.23-1.48	<0.001
	Confusion	1.36	1.20-1.54	<0.001
Chronic pulmonary disease	Core		*reference*	
	Core, fatigue, and cough	1.25	1.09-1.43	0.002
	Productive cough	2.17	1.97-2.39	<0.001
	GI symptoms	0.81	0.66-1.00	0.054
	Pauci-symptomatic	0.84	0.74-0.94	0.004
	Afebrile	1.48	1.33-1.65	<0.001
	Confusion	0.87	0.74-1.03	0.105
Asthma	Core		*reference*	
	Core, fatigue, and cough	0.82	0.69-0.98	0.028
	Productive cough	1.50	1.35-1.67	<0.001
	GI symptoms	0.99	0.81-1.18	0.915
	Pauci-symptomatic	0.62	0.54-0.72	<0.001
	Afebrile	0.94	0.83-1.06	0.334
	Confusion	0.78	0.64-0.95	0.013
Chronic kidney disease	Core		*reference*	
	Core, fatigue, and cough	1.05	0.91-1.21	0.509
	Productive cough	0.87	0.78-0.98	0.023
	GI symptoms	0.90	0.73-1.11	0.344
	Pauci-symptomatic	1.18	1.06-1.32	0.003
	Afebrile	1.01	0.90-1.13	0.883
	Confusion	1.09	0.94-1.26	0.276
Chronic neurological disease	Core		*reference*	
	Core, fatigue, and cough	1.69	1.45-1.95	<0.001
	Productive cough	0.92	0.80-1.06	0.238
	GI symptoms	0.51	0.38-0.68	<0.001
	Pauci-symptomatic	1.37	1.21-1.56	<0.001
	Afebrile	1.01	0.88-1.15	0.940
	Confusion	1.76	1.50-2.06	<0.001

	Cluster	Odds ratio (OR)	95% CI	P value
Malignancy	Core		*reference*	
	Core, fatigue, and cough	1.21	1.01-1.44	0.035
	Productive cough	1.28	1.11-1.46	<0.001
	GI symptoms	1.13	0.89-1.44	0.324
	Pauci-symptomatic	1.35	1.18-1.55	<0.001
	Afebrile	1.13	0.98-1.30	0.095
	Confusion	1.14	0.94-1.38	0.183
Chronic haematological disease	Core		*reference*	
	Core, fatigue, and cough	0.99	0.76-1.30	0.962
	Productive cough	1.01	0.83-1.24	0.885
	GI symptoms	0.72	0.49-1.05	0.088
	Pauci-symptomatic	1.00	0.82-1.23	0.975
	Afebrile	0.84	0.68-1.05	0.125
	Confusion	0.83	0.61-1.12	0.223
HIV	Core		*reference*	
	Core, fatigue, and cough	1.03	0.42-2.57	0.944
	Productive cough	1.58	0.91-2.73	0.103
	GI symptoms	1.97	0.96-4.02	0.063
	Pauci-symptomatic	0.95	0.46-1.95	0.887
	Afebrile	1.40	0.75-2.60	0.291
	Confusion	0.25	0.03-1.86	0.175
Chronic rheumatological disease	Core		*reference*	
	Core, fatigue, and cough	0.99	0.83-1.19	0.953
	Productive cough	1.05	0.91-1.20	0.509
	GI symptoms	1.24	1.00-1.54	0.053
	Pauci-symptomatic	0.97	0.84-1.11	0.622
	Afebrile	0.92	0.80-1.06	0.256
	Confusion	1.02	0.85-1.23	0.804
Dementia	Core		*reference*	
	Core, fatigue, and cough	1.58	1.38-1.82	<0.001
	Productive cough	0.48	0.42-0.56	<0.001
	GI symptoms	0.22	0.15-0.34	<0.001
	Pauci-symptomatic	1.15	1.02-1.29	0.089
	Afebrile	0.81	0.72-0.92	0.001
	Confusion	1.80	1.57-2.07	<0.001

	Cluster	**Odds ratio (OR)**	**95% CI**	**P value**
Malnutrition	Core		*reference*	
	Core, fatigue, and cough	2.20	1.61-3.01	<0.001
	Productive cough	1.21	0.89-1.66	0.225
	GI symptoms	1.39	0.82-2.33	0.220
	Pauci-symptomatic	1.77	1.34-2.34	<0.001
	Afebrile	1.47	1.10-1.97	0.012
	Confusion	2.45	1.78-3.38	<0.001
Chronic liver disease	Core		*reference*	
	Core, fatigue, and cough	2.09	1.58-2.77	<0.001
	Productive cough	1.20	0.94-1.52	0.142
	GI symptoms	1.20	0.83-1.73	0.338
	Pauci-symptomatic	1.35	1.05-1.75	0.019
	Afebrile	1.61	1.27-2.04	<0.001
	Confusion	2.16	1.57-2.97	<0.001
Diabetes	Core		*reference*	
	Core, fatigue, and cough	1.20	1.06-1.35	<0.001
	Productive cough	0.89	0.81-0.98	0.014
	GI symptoms	1.12	0.97-1.30	0.123
	Pauci-symptomatic	1.00	0.91-1.10	0.988
	Afebrile	1.08	0.98-1.19	0.108
	Confusion	1.09	0.95-1.24	<0.001

Supplementary Table 4. Restricted mean survival times adjusted for age.

Cluster	Sex	Mean difference (days)	95% CI (days)	P value
Core		*Reference cluster*		
Core + fatigue + confusion	Male	-1.9	-2.8 – -1.1	<0.001
	Female	-1.7	-2.8 – -0.6	0.002
Productive cough	Male	0.5	-0.1 – 1.0	0.085
	Female	0.5	-0.2 – 1.2	0.132
GI symptoms	Male	1.3	0.5 – 2.1	0.002
	Female	2.7	2.0 – 3.5	<0.001
Pauci-symptomatic	Male	2.5	1.9 – 3.0	<0.001
	Female	2.3	1.7 – 2.9	<0.001
Afebrile	Male	0.4	-0.3 – 1.0	0.258
	Female	0.3	-0.4 – 1.0	0.426
Confusion	Male	0.7	-0.3 – 1.7	0.158
	Female	1.2	0.1 – 2.3	0.038

Acknowledgements

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: during the conduct of the study; JW reports he is an employee of ZOE Global Ltd; TDS reports he has acted as a consultant for ZOE Global Ltd; PJMO reports personal fees from Consultancy, grants from MRC, grants from EU Grant, grants from NIHR Biomedical Research Centre, grants from MRC/GSK, grants from Wellcome Trust, grants from NIHR (HPRU), grants from NIHR Senior Investigator, personal fees from European Respiratory Society, grants from MRC Global Challenge Research Fund, outside the submitted work; and The role of President of the British Society for Immunology was an unpaid appointment but my travel and accommodation at some meetings is provided by the Society; AMD reports grants from Department of Health and Social Care,

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Data sharing

We welcome applications for data and material access through our Independent Data and Material Access Committee (https://isaric4c.net). The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination

ISARIC4C has a public facing website and twitter account @CCPUKstudy. We are engaging with print and internet press, television, radio, news, and documentary programme makers.

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