**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Wim Weber (chair); Jamie Kirkham (statistician); Tiago Villanueva; John Fletcher; Elizabeth Loder; Jin-ling Tang

Decision: Request revisions. Stats report from JK first

* Many editors felt that presentation needs to be improved. Please see the suggestions of Dr. Kirkham. Among the comments of the editors: Table 1 is very difficult to read and I didn't find the figures that useful. I'd like to see the standard table of baseline characteristics of patients by sex and age group that we see in every case series with data on comorbidities, hospitalizations and deaths.

**Reply:**

A new Table 1 has been added to display the baseline characteristics of patients as suggested by the manuscript committee. Previous Table 1 becomes Table 2, and clarifications have been added to aid in its interpretation. The figures have been extensively updated. The flowchart now demonstrates the division of the study cohort into three subsets based on testing strategy. The data that was previously presented in Figures 3 and 4 have been merged into a single Figure 3. The Results and Discussion sections have been extensively revised to improve the flow and clarity of the manuscript.

* Another editor noted that "In essence they have 3 populations, that were tested:

1. Clinically suspected cases and individuals at high risk of exposure.
3. A randomly chosen sample of 6782 Icelanders was offered testing via telephone text message on March 31 and April 1, 2020, of whom 2283 were included.

They give data for 1: 94.4 positiv per 1000 tests and for 2: 7 per 1,000.

They do not give data specified for group 3.

They give a mortality figure of 0.6% for the complete group, which is not very informative. A IFR calculation would be welcome on the unselected group (3).
Reply:

Our collaborators at deCODE genetics have provided additional data that have allowed us to differentiate persons diagnosed by the open-invitation population screening from those diagnosed by random population screening. Consequently, we are now able to report the data categorized by the three testing strategies. In line with the reviewers’ and editors’ suggestions, we have revised the Results section, providing additional focus on the three subgroups. None of the persons diagnosed by open-invitation population screening (146 patients) or random population screening (20 patients) died, and due to the small number of patients it is not prudent to calculate or report the case fatality rate for these subgroups. In the time since the manuscript was submitted, a seroprevalence study of SARS-CoV-2 in Iceland has been published in the New England Journal of Medicine (https://www.nejm.org/doi/full/10.1056/NEJMoa2026116). This publication provides an estimate of the infection fatality rate in Iceland. We have cited this publication in the revised manuscript.

In lines 22-23, page 23, we have added:

“In the recent seroprevalence study in Iceland, the infection fatality rate was estimated to be 0.3%.”

* We noted that this is one of the most complete country-level datasets available. The potential advantage of a study in a small population is the ability to screen everyone for symptoms or to test everyone and so get a clear picture of COVID-19 disease in a well defined cohort. The Diamond Princess provided this early on in the outbreak.

But we note here (as mentioned above, that the study sample is as ill defined with the usual mix of symptomatic community cases, asymptomatic contacts, volunteers and random sampling.

Reply:

We have revised the manuscript to detail the composition of the study sample with special emphasis on the testing strategies used. Additionally, large parts of the Results section have been revised in order to better communicate the differences in symptom progression among individuals diagnosed through the different testing strategies.

* Another editor queried the figure of 5% asymptomatic at diagnosis, 3% who remained asymptomatic. Is that 3% of the total, or of the 5%? We’d rather you state the % who were asymptomatic over the course of the infection (regardless of at diagnosis or not).

Reply:

The 3.1% refers to the total proportion of SARS-CoV-2-positive patients who were asymptomatic throughout follow-up. We have revised the relevant text in the abstract to clarify this finding, which now reads:
“At the time of diagnosis, 83 (5.3%) individuals reported no symptoms, of whom 49 (59.0%) remained asymptomatic during follow-up.”

* We liked the colored picture of how the symptoms evolve for the different age groups. It gives us a feel for how things evolve over time.

* Please include a declaration of patient or public involvement in the research in the methods section of the paper, and include a dissemination statement in the end matter. If for any reason there was no PPI please explain what your barriers to this were.

Here is BMJ Guidance on these matters:

Mandatory patient and public involvement reporting

The BMJ is encouraging active patient and public involvement in clinical research as part of its patient partnership strategy. This is research which is "co produced" with patients, carers, or members of the public. Patient involvement in this context is not about being a research participant, answering surveys, or being an interviewee. It encompasses setting research priorities, defining research questions and outcome measures, providing input into study design and conduct, dissemination of results, and evaluation.

To support co production of research we request that authors provide a short paragraph as a subsection within the methods section of their papers entitled Patient and Public Involvement detailing how they involved the patients and the public in their research. We request this to both encourage the movement and ensure that BMJ readers can easily see whether, and if so how, patients and the public were involved in the research. If they were not involved in any way this information should be formally documented in the Patient and Public Involvement section.

As co production of research with patients and the public is relatively new we appreciate that not all authors will have involved them in their studies. We also appreciate that patient / public involvement may not be feasible or appropriate for all papers. We therefore continue to consider papers where they were not involved.

The Patient and Public Involvement section should provide a brief response to the following questions, tailored as appropriate for the study design reported:

• At what stage in the research process were patients/public first involved in the research and how?

• How were the research question(s) and outcome measures developed and informed by their priorities, experience, and preferences?

• How were patients/public involved in the design of this study?

• How were they involved in the recruitment to and conduct of the study?
• Were they asked to assess the burden of the intervention and time required to participate in the research?

• In addition to considering the points above we advise authors to look at guidance for best reporting of patient and public involvement as set out in the GRIPP2 reporting checklist.

Link only https://drive.google.com/file/d/14vnXwTJ2CDn2KQsuNpuEnSwad69gc7dR/view

Reply:

We did not involve patients or representatives of the general public in the design, analysis or report of this study. This approach has not been incorporated in medical research policies in Iceland. Based on the rationale provided by the BMJ, patient and/or public involvement is likely to occur in the future. A declaration on patients or public involvement can be found on page 9, lines 13-14 of the Methods section and now reads:

“Neither patients nor the public were involved in the design, conduct, reporting, or dissemination planning of the research.”

Dissemination

Please confirm when and how results were (or will be) disseminated. Guidance for best practice in dissemination is set out in the following link and gives examples:

https://www.nihr.ac.uk/funding-and-support/documents/funding-for-research-studies/manage-my-study/How-to-disseminate-your-research/dissemination-guidance.pdf

The authors need to add a statement about dissemination with the other declarations like COI etc. Here they can just share how they plan to let people know about the paper, examples include: conference, poster, blog, social media, send to advocacy groups, press release, blog, posing on research website or adding to repository interviews, a companion opinion article in the BMJ or elsewhere etc. In addition how will you disseminate to patients and relevant communities. How were (or will) patients and the public be involved in choosing the methods and agreeing plans for dissemination of the study results to participants and wider relevant communities?

Reply:

Once the paper is published, dissemination of the findings will be carried out by issuing a press release that we anticipate will lead to domestic media coverage. The results will be shared on social media, both from individual authors and from our institutions, Landspitali–The National University Hospital and the University of Iceland. The results will be presented at medical conferences. Patients will not be involved in dissemination of the findings, but will have access to the results. A dissemination statement has been added to the manuscript, page 3, lines 13-19.
In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper. Please return a track changes version of the manuscript as well as a clean copy with changes accepted.

Comments from Reviewers
Reviewer: 1

Comments:

It is important for those of us who are faced with decisions related to sars-cov2 and covid-19 infection every day, to know both which are the most frequent symptoms or that allow us to predict a positive test result or to know what percentage of the population She is generally asymptomatic or has atypical symptoms. This allows us to make better decisions in the “pre-test” for the definition of a suspected case or to make decisions not based on symptoms but rather on population testing or according to the epidemiological link and establish strategies for epidemiological decision making. All new knowledge about these two “variables” is well received by the medical community and decision makers. Another problem we face is the changing definition of a suspected case according to the epidemiological situation, which underwent repeated variations as the development of this new disease was understood a little better.

In this article, we can observe these three perspectives, since there are actually three different populations in this cohort-type, population-based study, carried out through the telemedicine system. These two populations are through the population screening type test or “population screening” and another directed through different definitions of suspected cases of the symptom type test directed at “targeted testing”. One of the interesting aspects of this work is that it allows to show some light on patients with atypical, asymptomatic symptoms or who do not meet the traditional definitions for testing, since it includes those carried out in a population screening or screening study and on another side to know the evolution and the weighting of the symptoms according to the evolution.

The point is that the initial research question is not what are the most frequent symptoms and their evolution, but if the presentation (asymptomatic, mild, moderate or severe) is indexed with the evolution and presentation of the disease. . The same different baseline risk scheme should be applied to the body of the article and moved to the conclusions given that the questions are much more varied: "population screening"

Reply:

We thank the reviewer for this summary and suggestions for improvement, which are mirrored in the suggestions of the BMJ manuscript committee. As noted in the reply to the manuscript committee, we have divided the study cohort according to testing strategy, and the Results section has been revised in parallel with the change in approach.

What percentage of the asymptomatic population is positive and which of them presents atypical symptoms (not defined by WHO for example), and how is the evolution of symptoms and disease in this subgroup of the population?
Unfortunately, the data available for the current study are insufficient to directly answer the question of what percentage of the asymptomatic population was SARS-CoV-2-positive. Those diagnosed by targeted testing were tested because of clinical symptoms and the open-invitation population screening did not exclude symptomatic individuals. Of those diagnosed by random population screening, only 6 of 20 SARS-CoV-2-positive patients were asymptomatic at diagnosis. None of these 6 individuals developed symptoms during follow-up. Those who had a negative test result were not enrolled in the telehealth service, and were therefore not interviewed with regard to the presence of symptoms. We have extensively revised a paragraph in the Discussion section that pertains to this comment, page 21 lines 10-18 now reads:

“The true proportion of SARS-CoV-2-positive persons who never develop symptoms can be estimated by longitudinal follow-up of individuals diagnosed by random population screening. In the current study, 6 of the 20 (30%) individuals diagnosed by random population screening never developed symptoms. This finding is supported by a recent seroprevalence study in Iceland that found that 44% of individuals with antibodies against SARS-CoV-2 had either not undergone RT-PCR testing or had tested negative, suggesting only mild or no symptoms among this group. A potential limitation of the random screening approach are uncertainties regarding the sensitivity and specificity of RT-PCR for detection of SARS-CoV-2.”

We have added a sentence that clarifies the prevalence of atypical symptoms among persons who did not meet WHO or CDC criteria. Page 17 lines 7-10 of the Results section now reads:

“Among persons who did not have symptoms consistent with the WHO or CDC criteria at diagnosis, the most common symptoms were headache 140 (37.6%), rhinorrhea 128 (34.4%), dysosmia 123 (33.0%) and dysgeusia 122 (32.8%), with 241 (64.6%) individuals experiencing at least one of these symptoms.”

"Targeted screening" how does the case definition influence the severity of the disease detected?

Reply:

Targeted testing was performed at the discretion of the ordering physician based on clinical suspicion of COVID-19. The symptoms did not have to meet the WHO and CDC case definitions and liberal testing strategy was encouraged by infection control authorities, resulting in widespread testing in Iceland. As shown in the supplemental material, those who were later admitted to hospital had more symptoms early in the disease course.

What is the baseline risk detected through case definitions?

Reply:
As noted above, the WHO and CDC case definitions were not a prerequisite for obtaining a test for SARS-CoV-2. We suspect that the reviewer may be using “case definitions” in reference to the different testing strategies (targeted testing, open-invitation population screening or random population screening) as suggested by other reviewers and the manuscript committee. We have revised the Results section to better clarify the progression of symptoms among patients diagnosed through the different testing strategies.

How is the evolution of the symptoms detected through this strategy?

Reply:

Monitoring of symptoms involved frequent structured telephone interviews by a nurse or a physician, through which the patient’s clinical status was evaluated. This is clarified in the Methods section, page 10, lines 19-22, and page 11, lines 1-5:

“A checklist of 19 specific symptoms was used during the initial and all subsequent interviews. The list of symptoms was developed based on findings reported in the literature at the time when the telehealth monitoring was being launched and with respect to symptoms reported by the first 200 Icelanders who contracted COVID-19. The list was subsequently refined, taking into account symptoms described by patients during the early interviews and was formally introduced on March 17. From this point onwards the checklist remained unchanged. Furthermore, the patients were asked during every interview if additional symptoms were present.”

The hypothesis could be that through population screening we could make relevant epidemiological decisions, while targeted screening would allow us to detect severity of the individual patient.

The proposal of the work is interesting, although there is a risk of potential loss of follow-up given the form of follow-up of this cohort, for which adherence and loss of follow-up are unknown, especially in screening-type population testing individuals. On the other hand, some description data of the tested population and the comparison between the strategies used for the testing of patients are missing. On the other hand, the results of this study could be generalizable if we knew the viral circulation and the epidemiological status in which the tests were developed, or how they varied over time.

Reply:

All patients who tested positive for SARS-CoV-2 in Iceland, regardless of testing strategy, were placed in isolation, enrolled into telehealth monitoring and were contacted via telephone daily to every fourth day, depending on the severity of symptoms. Patients were only eligible for discharge from both isolation and telehealth monitoring if at least 14 days had passed from the date of PCR diagnosis and they had been symptom-free for seven or more consecutive days. Once patients were judged by a nurse to have met these criteria, they were released from isolation or monitoring following a discharge interview by a physician, in which the discharge
criteria were re-evaluated. Hence, there was no known loss of patients to follow-up, and no reason to believe that undetected loss to follow-up had occurred. We agree with the suggestion made by this reviewer and others that a better description of baseline demographics adds clarity, and we have provided such data in a new Table 1 and revised the Results section accordingly.
Reviewer: 2

Comments:

• Are the questions the paper addresses relevant and important to patients and/or carers?

Main Question: What is the frequency and progression of various symptoms experienced by patients with COVID-19?

Yes. Knowing the symptoms can both help self-diagnose in order to get medical attention, self-isolate, and stop the spread of . Only half of the individuals with covid-19 (referred to in the paper and henceforth as “patients”) experience a sore throat and ⅔ of patients experienced a non-productive cough. 33 percent experienced a productive cough although it does not appear that these populations are separate. Therefore, know the progression of the symptoms only up to day 14 of evaluation is somewhat helpful.

Days from symptoms onset not as useful than from exposure date which could have been determined with the contact tracing data and telehealth. The standardization is helpful for the analysis of the 3 population

Reply:

We agree that using the date of exposure may add information regarding interpretation of the natural history of COVID-19, if readily available for all diagnosed cases. However, as known exposure was never a requirement for testing in Iceland, it was frequently unknown at the time of diagnosis. Known exposure was even less common among those who were diagnosed through open-invitation population screening and random population screening. The contact tracing team at the Department of Civil Protection and Emergency Management interviewed every individual who was found to be SARS-CoV-2 positive, and traced their contacts as much as 4 days prior to diagnosis, placing these contacts in quarantine. Their database was explored, revealing that only 510 of the 1797 SARS-CoV-2-positive patients could be linked to a known exposure. However, the reliability of these data has not been examined and their analysis requires a complex approach that is beyond the scope of the current study.

We have revised the description of the testing protocols for clarity. Page 10, lines 1-7 now reads:

“Targeted testing began on January 31, 2020, and included clinically suspected cases and individuals at high risk of exposure, though exposure was not a requirement for testing. Open-invitation population screening began on March 13, 2020, and was available to all Icelandic residents who were not in quarantine and did not have symptoms that prompted targeted testing. Finally, a randomly chosen sample of 6782 Icelanders was offered testing via telephone text message on March 31 and April 1, 2020.”
This is an epidemiological study that has limited information relevant for patients or carers.

Was the question answered? Partially.

• Are there topics or issues that are missing, or need to be highlighted more?

The authors claim to have a “complete clinical spectrum for covid-19’ however, the authors used a standardized covid questionnaire highlighting and tracking19 symptoms. Other symptoms that have been reported by patients include more than these 19 symptoms. Another questionnaire should have been included through the telehealth and hospital records. Other symptoms, even if rarer than the standardized symptoms, are part of the symptomatic progression and the clinical picture of COVID-19.

Reply:

We agree that when standardized questionnaires are used there is invariably a risk of underreporting of rare symptoms, and that our knowledge of the symptoms of COVID-19 has accumulated throughout the pandemic. The list of symptoms was developed based on findings reported in the literature at the time when the telehealth monitoring was launched and symptoms reported by patients in Iceland before the standardized data entry form was established (the first 200 patients). Patients were specifically asked about the 19 symptoms during each interview, which allowed us to accurately quantify the proportion of individuals experiencing these symptoms and report how this changed over the illness period. Furthermore, during the interviews the nurse or physician did not only record the predefined 19 symptoms, but also carried out a comprehensive assessment of the patient's physical and mental state and provided information and support. A free text area was provided for documentation of additional symptoms. This has been clarified in the text on page 10, lines 19-22, and page 11, lines 1-5:

“A checklist of 19 specific symptoms was used during the initial and all subsequent interviews. The list of symptoms was developed based on findings reported in the literature at the time when the telehealth monitoring was being launched and with respect to symptoms reported by the first 200 Icelanders who contracted COVID-19. The list was subsequently refined, taking into account symptoms described by patients during the early interviews and was formally introduced on March 17. From this point onwards the checklist remained unchanged. Furthermore, the patients were asked during every interview if additional symptoms were present.”

Long-term symptoms are not included as no long term follow up with patients was performed. Other papers (Carfi et al 2020) have very clearly observed long term symptoms in COVID-19 and yet only a few weeks of observation were recorded during the main symptomatic occurrence.

Reply:

Since the objective of this study was to characterize the clinical spectrum of the acute phase of COVID-19, the symptoms were collected during the acute infection only. It has become
apparent that a subset of patients experiences long standing symptoms after recovering from the acute illness associated with COVID-19, as described by Carfi et al. Though this was not within the scope of our study, we have highlighted this limitation in the Discussion section. Page 25, lines 3-7 now reads:

“Finally, our study was concerned with the symptomatology of the acute phase of COVID-19. It has become apparent that patients may experience prolonged symptoms following their initial infection. Telehealth monitoring was discontinued after the resolution of the acute illness, and we therefore cannot characterize the nature of long-term symptoms of COVID-19.”

How long patients were thought to be spreading the virus without symptoms could have been addressed with this population data. This would be answering an even more important questions for patient and the population of potential patients, especially those with pre-existing conditions. Population screening showed that 40% of covid-19 positive individuals did not have symptoms at the time of testing.

Reply:

The time period during which asymptomatic individuals could have been transmitting the virus cannot be established in this study since the date of exposure is only known for the minority of patients. We can however report the number of individuals that were asymptomatic. One could then speculate that if these patients had not been diagnosed and isolated, they might have spread the virus. We have added a paragraph that describes what proportion of patients diagnosed by random population screening were asymptomatic at diagnosis. The paragraph is on page 15, lines 22, and page 16, lines 1-9:

“Eighty-three (5.3%) persons reported no symptoms at diagnosis, which was more commonly noted among those diagnosed through open-invitation population screening (n=32, 23.7%) and random population screening (n=6, 30.0%), as compared with individuals diagnosed by targeted testing (n=45, 3.2%). Of the persons who were asymptomatic at diagnosis, 49 (59.0%) did not develop any symptoms throughout the telehealth monitoring, while the remaining 34 (41.0%) individuals developed symptoms after a median of 3 days (IQR, 3-4.75). All persons diagnosed by random population screening who were asymptomatic at diagnosis remained so during follow-up, compared with 19 (59.4%) individuals identified by open-invitation population screening and 24 (53%) diagnosed by targeted testing.”

• Is the treatment or intervention suggested or guidance is given something which patients/carers can readily take up? or does it present challenges?

This is a descriptive study of a population. It does not suggest anything to the population but does suggest the Icelandic model of COVID-19 tracing as the correct type. This presents challenges as Covid-19 has been politicized and many are not willing to implement such a rigorous method of contact tracing and population testing. It also must be noted that Iceland is
an island with a small population and a repeated measure in a larger and more ethnically heterogeneous population would result in different data. Patients do not benefit from their suggestion to take up the Icelandic model as it is on governments to do so.

Comment:

**Reply:**

The Icelandic response to the COVID-19 pandemic appears to have been successful as the outbreak subsided surprisingly soon after implementation of counter-measures. We agree that these measures might not be effective in other populations as mentioned by the reviewer. Page 24, lines 3-5 now reads:

“Nevertheless, these differences and the homogenous population in Iceland may limit the generalizability of our findings to other nations and geographical areas.”

• Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered?

Yes the outcomes described are important, yet there is more that could have been considered with the present data. The population sampling revealed that for those whom tested positive, 22% had no symptoms. This leaves a certain percent of the population (age cohort the study does not explicitly state) that is silently spreading the virus. How long patients were thought to be spreading the virus without symptoms could have been addressed with this population data. This would be answering an even more important questions for patient and the population of potential patients, especially those with pre-existing conditions.

**Reply:**

We have revised the Results and Discussion sections to better communicate this information as described in a previous comment to the reviewer.

• Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/carers?

With the data, the researchers could have determined a possible date of infection (contact tracing) and determining how long that was before patients selected for medical intervention would have strengthened the paper’s answer to it’s primary question. Symptoms do not simply start at the day of diagnosis and last for the 14-20 day observation period.

As well, more information should have been gathered about the patients long term outcomes using telehealth. This would allow for the knowledge of disease progression as cited Carfi et al (2020).
Reply:

Regarding the time from exposure to diagnosis, we refer to our previous responses and corresponding revisions of the manuscript.

We do agree that symptoms do not start on the day of diagnosis and have made efforts to avoid implying this throughout the manuscript. As reported in the paper, the median time from symptom onset to PCR diagnosis is four days. Most patients were enrolled into the telehealth monitoring service on the day of diagnosis. We are unfortunately unable to assess the time of exposure as highlighted in our previous response.

During the first enrollment interview, patients were specifically asked about the date when they first noted symptoms and were asked to list all symptoms that they had experienced from the date of symptom onset to the enrollment interview. The patients were then monitored with frequent telephone interviews (daily to every fourth day) until 14 days had passed from the PCR diagnosis, and they had been symptom-free for at least 7 days. What constituted being symptom-free was left to the discretion of the physician who managed the discharge interview. Understandably, the determination of active symptoms varied slightly between physicians and over time. In general, symptoms that are associated with viral spread (cough, rhinorrhea, vomiting and diarrhea) or generalized symptoms (fever, chills, myalgia) were approached with caution and required prolongation of the isolation.

Because of the requirement for a 7-day symptom-free period, we can be fairly confident that this paper adequately covers the symptomatology of the acute phase of COVID-19 among patients who do not require hospital admission. In essence, the observation period was dynamic, and those who experienced persistent symptoms were observed for a longer time period (25% of the cohort was followed for 18-54 days). In addition to this, all the statistical methods used to analyze the data were selected to complement the way in which the data were collected, in order to describe the symptom progression as accurately as possible.

We agree that the long-term symptoms experienced by many patients with COVID-19 need further study. Though this was not within the scope of our study, we have highlighted this limitation in the Discussion section. Page 25, lines 3-7 now reads:

“Finally, our study was concerned with the symptomatology of the acute phase of COVID-19. It has become apparent that patients may experience prolonged symptoms following their initial infection. Telehealth monitoring was discontinued after the resolution of the acute illness, and we therefore cannot characterize the nature of long-term symptoms of COVID-19.”

• Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so?
There was no patient involvement in the paper. A way that could have been easily integrated was to listen to patients long term symptomatic improvement or lack of improvement through continuing telehealth survey. Lastly, allowing for the suggestion of symptoms other than the symptoms that have been previously assessed in COVID-19 would have brought patient-centred information which has already been published in other studies (Carfi et al 2020)

Reply:

Co-production with patients is addressed in the response to the same comment made by the BMJ manuscript committee above.


Reviewer: 3

Comments:

The clinical spectrum of COVID19

The paper addresses an important aspect of COVID19 epidemic as little is known on the clinical spectrum of this illness. The study was well done and has important information not available in many other papers (due to design). The number of participants allow a good data analysis and to answer many questions still pending

Abstract

Is well written but some important information is missing like the prevalence of hospitalized participants, critical cases and death. The COVID lethality among all diagnosed groups would be welcome.

Reply:

The principal aim of the study presented in this manuscript was to describe the clinical symptoms and symptom progression of COVID-19 using longitudinal, prospectively collected data from a population-based sample. Data regarding hospital admission and mortality is presented in the Result section of the paper. However, space limitations preclude adding this information to the abstract. Page 15, lines 1-3 now read:

“In total, 101 (5.6%) patients were hospitalized, 27 (1.5%) were admitted to an intensive care unit and 16 (0.9%) required mechanical ventilation. The median length of hospital stay was 8 days (IQR, 3.5-19) and 10 (0.6%) patients died.”

The study has enough data to give the readers more detailed information on asymptomatic cases, which are very important for disease transmission and the most prevalent (non-WHO non-CDC) symptoms associated

Reply:

We have added a more thorough description of asymptomatic and presymptomatic patients in the study cohort. In line with the reviewer’s suggestions, we have revised large parts of the Result section. However, we do not have useful data on transmission of the infection and therefore cannot comment on the relative importance of symptomatic and asymptomatic spread, as highlighted in our response to reviewer 2. Additionally, page 17 lines 7-10 of the Results section now reads:

“Among persons who did not have symptoms consistent with the WHO or CDC criteria at
diagnosis, the most common symptoms were headache 140 (37.6%), rhinorrhea 128 (34.4%), dysosmia 123 (33.0%) and dysgeusia 122 (32.8%), with 241 (64.6%) individuals experiencing at least one of these symptoms.”

Key points

The possibility of transmission by asymptomatic young children was not highlighted

Reply:

A relatively small number of children (2299 below the age of 10) were tested for SARS-CoV-2 and few (n=60) were positive. Of those, three were diagnosed by open-invitation population screening and none were diagnosed by random population screening. Only four of the 60 SARS-CoV-2-positive children were asymptomatic at diagnosis, and these were diagnosed by targeted testing. Because some degree of suspicion of COVID-19 was needed to prompt testing of an individual, symptomatic patients are likely to be overrepresented among those diagnosed by targeted testing. Inference with respect to the true asymptomatic proportion of children, or their potential transmission is not attainable using our data.

Methods

Protocol included all patients who tested positive for SARS-CoV-2 between February 27 and April 30, 2020

On March 17, a standardized data entry form was built directly into the national electronic medical records

Diagnosis: RT PCR and TaqMan 2019-nCoV Assay from Thermo Fisher Scientific

In this paper, authors describe the analysis of prospectively collected data on all SARS-CoV-2 positive patients in Iceland and characterize the epidemiology and full clinical spectrum of COVID-19 in a nationwide cohort.

Patients were asked whether they had experienced any of the 19 symptoms from the time of symptom onset to the time of the interview.

Question: were patients able to tell other symptoms not included in the list???

Reply:

The telehealth service was established to provide care to patients who were isolated at home with COVID-19. The purpose of the checklist was to support the clinical care provided to patients at the COVID Outpatient Clinic and grade the severity of illness. The telephone interview was otherwise conducted like any other patient contact and patients were encouraged to discuss all their concerns, including other symptoms and experiences involving COVID-19.
The nurse or physician was provided with an option to record additional information about symptoms in a free text area in the patient’s medical record. The main strength of our analysis is the systematic collection of standardized data on clinical symptoms. Information in the free text area was not standardized and was recorded at the discretion of the interviewer. Therefore, we do not have reliable information on symptoms other than those included in the checklist. Some patients described chest tightness or pain, a burning sensation when breathing and calf pain.

Question: were some of patients enrolled in clinical trials for COVID19? If yes how did you analyse this fact?

Reply:

None of the patients were enrolled in clinical trials of COVID-19.

Results

Could authors comment more deeply the asymptomatic cases among young people? Specially for 0-5 and after 5 and even young adults? These are a very important groups as it seems that many children under 5 are asymptomatic during COVID19 and this is a special issue for transmission to older people at home. Could you show the absence of signs and symptoms according to age?

Reply:

We do not believe that our data provide an adequate estimate of the proportion of children who were asymptomatic. Only 1184 children five years of age or younger were tested for SARS-CoV-2, of whom only 29 were positive. Two of these were diagnosed by open-invitation population screening, while the remaining 27 were diagnosed by targeted testing. Only two were asymptomatic and they were both diagnosed by targeted testing. As explained in the response to a previous comment, patients diagnosed by targeted testing cannot be used to infer the true asymptomatic proportion of patients. As described in the Discussion section, our best estimate of the asymptomatic proportion is based on those diagnosed by random population screening, of whom six (30%) of the 20 patients were asymptomatic. The sample size not support separate estimates by age group.

Have you information on pregnant women? I have not seen any data on this

Reply:

Of the 1797 patients, 20 were pregnant. None were admitted to hospital and all survived.

Could you describe the symptoms that were not associated with COVID-19 according to the CDC and WHO? Will be interesting to see this and the prevalence according to age as well

Reply:
We agree that this information is of interest and have added it to the manuscript on page 17 lines 7-10 of the Results section:

“Among persons who did not have symptoms consistent with the WHO or CDC criteria at diagnosis, the most common symptoms were headache 140 (37.6%), rhinorrhea 128 (34.4%), dysosmia 123 (33.0%) and dysgeusia 122 (32.8%), with 241 (64.6%) individuals experiencing at least one of these symptoms.”

Finally, the paper is of good quality and an opportunity to have missing information on literature
Reviewer: 4

Comments:

• Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

Overall, this is a thorough analysis on symptom progression in generally milder cases of COVID-19. Agree with the suggestion that this could be useful for prognostics and reinforcing our overall understanding of this disease. It is understood that there has been a worldwide collective effort to study COVID-19 as quickly as possible; some of this information may soon begin to become redundant, but until then, our repository of knowledge is still being built.

• Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it?

This is work is appropriate for a general journal by the large encompassing implications the results show. Essentially, this shows the best representation of an entire country as of yet. Albeit, this country is relatively small, and may not be representative of others, in many ways, as the authors noted it is also comparable. It may be useful to clinicians, researchers, educators, patients, and policy makers, possibly in that order. Altogether, there are many who would be interested in this type of research. Some may consider this also appropriate for a journal related to Infectious Diseases.

• Scientific reliability

Temporality between symptoms and outcome is important to show. This manuscript does that well. While shown in the figures, if not listed in the text completely. Investigation for adverse outcome should be made as early as possible to have the most benefit.

• Research Question - clearly defined and appropriately answered?

The research questions related to the clinical spectrum of COVID-19 is quite broad, and in ways cumbersome to grasp entirely. This is limited by available data to conduct the analysis; however, compared to other similar studies this is one of the largest data set, and most unique. Still this may not be inclusive of all. Again, to the point on timing of data for such a question to be answered, this is well placed.

• Overall design of study - adequate?

45,105 tested, including targeted and screening. 1,797 tested positive. 1,564 included in analysis. Some further explanation can be made if as to how the authors decided to discharge a
patient from telehealth monitoring. Our own experience has been convoluted and constantly requiring reassessment. The authors mention patients were discharged only after 7 consecutive days without symptoms. This is different from current, or even previous CDC guidelines. It may be worth discussing how this criterion was developed. As we now know, symptoms may persist well beyond the period of infection. Were some symptoms given greater weight than others (i.e. fever or respiratory symptoms as listed in CDC guideline)? Some symptoms may even arise after infection, such as post febrile telogen effluvium, especially in critically ill patients.

Reply:

Based on the limited information available when the pandemic hit Icelandic shores, we decided that all individuals be isolated for a minimum of 14 days from the date of a positive PCR swab for SARS-CoV-2. Additionally, patients were required to be symptom-free for at least 7 days before being released from isolation.

Early in the pandemic, many countries were basing their discharge criteria on the individual being PCR negative for SARS-CoV-2, with some even requiring two negative results 24 to 48 hours apart. We did consider this approach, but following a thorough review which included expert opinion of a panel of infectious disease consultants and virologists, we opted for relying on clinical discharge criteria. Despite the use of defined criteria to guide the discharge decision, the threshold of what was considered persistent symptoms varied slightly between physicians and over time. However, symptoms that are associated with viral spread (cough, rhinorrhea, vomiting and diarrhea) or generalized symptoms (fever, chills, myalgia) were approached with special caution and required prolongation of isolation. We have added this information to the Methods section.

References:


• Participants studied - adequately described and their conditions defined?

Thank you to the authors for providing demographic information on participants studied. Seeing that this was within a single payer system in a country with population around 364k, this does point toward possibility of collection bias with analysis heavily reliant on an ethnically homogenous population. It may be useful to include more information on description for epidemiologic purposes. This paper is limited to age and sex. Consider adding race, smoking status, pregnancy status, and other risk factors (if available) as have been highlighted by CDC:

Reply:

We have no reason to suspect that sampling bias was associated with the study data. However, we understand the point made by the reviewer that the results may not be generalizable to other populations due to the homogeneity of the Icelandic population. This notion can certainly not be excluded and is addressed in the revised version of the manuscript. We also agree with the reviewer that providing additional baseline variables would allow readers to compare the study population to their own, in order to assess the relevance of our results to their population. We have added a new Table 1 that displays these variables. Page 24, lines 3-5 now reads:

“Nevertheless, these differences and the homogenous population in Iceland may limit the generalizability of our findings to other nations and geographical areas.”

• Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical?

Considering the mild severity of symptoms, and illness, it seems the patients were contacted very frequently. Also, the method of contact could be added. Was this video, telephone? Why or why not.

Reply:

The frequency of patient contacts ranged from daily to every fourth day, depending on their risk score and clinical severity. All interviews were conducted via telephone as equipment for video consultations was not available in our clinic. Nevertheless, we believe that telephone would have been selected as the communication modality, even if video technology had been available, as many of our patients were older and might have had technical difficulties using video technology.

Additionally, it might be beneficial for the authors to state why they chose April 30, 2020 as the end date for this study, if this date was chosen because there was a decrease in cases as we witnessed in some parts of the world.

Reply:

The data were extracted and prepared for statistical modeling on May 22, 2020, and included all patients who were diagnosed with COVID-19 until April 30. This date allowed sufficient follow-up time for individuals diagnosed in the final days of the study period. Only 12 patients were found to be SARS-CoV-2-positive between May 1 and June 15, and thus we did not feel that extending the sample collection period would be beneficial.

• Results - answer the research question? Credible? Well presented?
The authors mention all data regarding symptoms was patient reported. How did they list the 19 symptoms, were these prompted, or all unprompted and categorized later? Analysis of symptoms, and descriptions is very thorough. Will be interesting to see more of this, as to how certain symptoms were associated with certain outcomes (hospitalization, etc).

Reply:

The standardized data entry form (checklist) was built directly into the national electronic medical record, as was the software that tracked which patients required interviews each day based upon the risk score and clinical severity documented in previous interviews. The electronic template required the healthcare provider to document the date and time of the interview, the trajectory of the patient’s overall clinical status, whether the patient was anxious, and the presence or absence of each of the 19 symptoms. The healthcare provider specifically enquired about each symptom, discussed this with the patient, interpreted the answer and recorded the presence or absence of the symptom. Free text areas were available for documentation of additional symptoms or for further clarification of the findings or description of the patient’s condition. The symptoms were not categorized later, though we do present two aggregate symptoms in the manuscript: any cough (productive and non-productive cough) and any dyspnea (dyspnea on exertion, dyspnea at rest and shortness of breath). This has been clarified in the text, page 10, lines 19-22, and page 11, lines 1-5:

“A checklist of 19 specific symptoms was used during the initial and all subsequent interviews. The list of symptoms was developed based on findings reported in the literature at the time when the telehealth monitoring was being launched and with respect to symptoms reported by the first 200 Icelanders who contracted COVID-19. The list was subsequently refined, taking into account symptoms described by patients during the early interviews and was formally introduced on March 17. From this point onwards the checklist remained unchanged. Furthermore, the patients were asked during every interview if additional symptoms were present.”

Subgroup analysis is further hypothesis generating, and may be useful to discuss – factors such as load effecting adverse outcome. Also differences is factors prior to infection (demographic / comorbidities), and those after infection (biomarkers), as mentioned above. Though this data may not be available, and that’s reasonable considering the setting.

Reply:

We agree that subgroup analysis can be viewed as hypothesis generating, and have collected additional data to present several subgroups of patients. Furthermore, we describe the basic demographics of the cohort, categorized by the three testing strategies. The data analyzed for this study did not include biomarkers, viral load etc.

• Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?
Biases and limitations are well described. There could be some further mention on limitations of this data by race, ethnicity, and socioeconomic, possibly being fairly homogenous.

Reply:

We have addressed the homogeneity of the Icelandic population in the paragraph featuring the study limitations in the Discussion section.

Discussion of other risk factors is helpful to review, such as those listed in above link at CDC; cancer status etc, and which type of adverse outcome is associated. The authors did well to categorize the symptom sets for ease of understanding (generalized, lower respiratory, GI, etc).

Reply:

We have added a new Table 1 which describes expanded baseline characteristics of the study population. Previous Table 1 becomes Table 2. See also the response above.

• References - up to date and relevant? Any glaring omissions?

None noted. To that end, I would recommend to ensure that none of the publications that ended up in the final review was retracted. Here is a list of retracted COVID-19 papers mentioned on Retraction Watch (https://retractionwatch.com/retracted-coronavirus-covid-19-papers/).

• Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?

Yes, will be useful information for clinicians and researchers alike. This again reinforces the understanding that the majority of COVID-19 patients experience mild symptoms.
Reviewer: 5

Comments:

Stats comments.

This is an interesting dataset but I don’t think the results are presented in the best possible way. My suggestions mostly involve improving the presentation of the data within the manuscript.

1) The study contains 3 testing protocols; 1) target testing, 2) open-invitation population screening and 3) random populations screening.

a) The results section do not separate the results by these three testing protocols. I think it would be hugely beneficial if the authors could present the results this way and the authors should consider this throughout. This is largely because the rates will be very different for each of these protocols. The random sample (protocol 3) is the only group that provides an unbiased estimate (the rates are likely to be higher for the other 2 protocols). This should be better reflected in the flow diagram (Figure 2) and deserves comment.

Reply:

This comment has been made by several other reviewers and the manuscript committee. Please see our response to their comments.

We agree with the approach outlined by the reviewers and the manuscript committee. Comparing individuals diagnosed by the three testing strategies is limited by the large difference in the size of the groups. Though the majority (29,785) of tests were performed as part of population screening, only 3924 were done in the random population screening cohort (participation rate 3924/6782; see below), and of those, only 20 were SARS-CoV-2-positive. The open-invitation population screening cohort consisted of 187 patients (out of 26,762 tested), whereas 1619 patients (out of 16,750 tested) were diagnosed through targeted testing. While we do agree that the presentation of the results should reflect the subgroups, we believe that this should be limited to descriptive comparisons, as the statistical models will perform poorly when applied to subgroups comprised of few individuals. We have made changes to Figure 2 and rewritten part of the Results section to better reflect the suggested subdivision of PCR positive Icelanders, taking into account the stated caveats.

b) In relation to protocol 3 and point a), the authors report that only 2283/6782 (about a third) were included. Can more insight be given into why this was and the potential impact on the analyses.
Reply:

The reviewer is referring to page 10, lines 5-7 of the original manuscript. This sentence describes the number of individuals in the greater Reykjavik area who were invited for random population testing by deCODE genetics. We do not possess information about individuals who declined to participate in the random screening. It is possible that individuals who had symptoms and were in quarantine or isolation at the time of invitation, did not participate due to fear of exposing the research staff. This could potentially bias downwards the estimated incidence of undetected COVID-19 in the population and bias upwards the asymptomatic proportion among those who tested positive. Conversely, it is also possible that individuals who suspected they might have COVID-19 for any reason were more likely to accept the invitation to participate than those who did not, which would bias upwards the estimated incidence and downwards the asymptomatic proportion. It is difficult to determine which of these possibilities, if any, played a role.

In response to the suggestions made by the editorial team and the reviewers, we approached deCODE genetics and obtained data that revealed to us which patients were diagnosed by random population screening and which ones were diagnosed by open-invitation population screening, whereas previously we were only able to ascertain that patients were diagnosed by population screening. We had previously cited the report by Gudbjartsson et al (https://www.nejm.org/doi/full/10.1056/NEJMoia2006100), that describes the random population screening in Iceland and was published shortly after the study sample had been invited to participate. In this publication, the authors report that 2283 of 6782 invited persons participated (a rate of 33.7%) and that 13 were found to be SARS-CoV-2-positive. Having obtained the data from deCODE genetics, we are now able to report that the final participation rate was 58% (3924 of 6782) and that a total of 20 were SARS-CoV-2 positive.

c) As with many of these descriptive COVID studies, the real value in the interpretation for the readers comes from an understanding of the patient demographics. It is unclear what a patient demographic details were collected in this study (though there is a suggestion these were collected in the data collections section and during interviews) but could these be tabulated in the MAIN results by testing protocol in the main manuscript

Reply:

We agree with the reviewer and note that a similar comment was made by other reviewers. We have added a new Table 1 that depicts the demographics, clinical characteristics and symptoms among the study cohort, categorized by the testing strategy and setting (targeted, open-invitation and random testing).

2) Symptoms:

a. a 19 symptom checklist was used. Was this list exhaustive and how was it developed – could the participants add additional symptoms?
Reply:

The same comment was made by Reviewer 3. Please see our response above.

b. Based on symptom documented, patients were classified into severity categories – who did this classification, was there good reliability?

Reply:

Both the risk categories (based on age and underlying conditions) and clinical severity categories were created as a clinical tool to triage patients into appropriate levels of care. In late February 2020, no quality data for triaging COVID-19 patients according to clinical severity were available, and thus the definitions were a consensus decision made by physicians at the COVID Outpatient Clinic and infectious disease consultants, and were subsequently refined based on the experience that accumulated from managing the first several dozen cases. Those with a higher risk and clinical severity categories, received more frequent follow-up interviews, and their interviews were conducted by a physician when possible. Thus, the severity categories were reliable for this purpose. This is explained in more detail in an article describing the Icelandic response to the pandemic (https://onlinelibrary.wiley.com/doi/full/10.1111/joim.13135).

c. Table 1 is mentioned in the methods section but it is actually a result. I didn’t find this table that useful in its current state. What are the numerators and denominators? Which testing protocol did they belong to? What is the cumulative incidence? Should you not just be presenting n (%) here rather than CIs – it’s unclear what the CI’s mean here?

Reply:

Table 1 (now Table 2) demonstrates the prevalence of specific symptoms at certain time points during the illness and the cumulative incidence of these symptoms. Since interviews were generally not conducted every day, the numbers presented are results of the cure-mixture model for the prevalence and the non-parametric Turnbull estimator for the cumulative incidence. Thus, we also present confidence intervals from these models. This has now been explained in detail in a footnote to Table 1. While some of these results are presented in figures in the main manuscript and supplemental file, we believe that this tabulation gives a clear overview of the data on symptoms and therefore have decided to leave it in the manuscript. Since there were few individuals in the random and open-invitation groups, we do not feel it is appropriate to present these data separately for the groups.

3) Can the authors explain in a bit more details what a ‘parametric cure-mixture models’ is? How did the modelling take into account participants with multiple tests? The results suggest some participants must have tested positive more than once. I think there is value in discussing these.

Reply:
The parametric cure mixture models were fitted in R statistics 3.6.6. using the flexsurvcure package (https://cran.r-project.org/web/packages/flexsurvcure/index.html). The aim of using these models was to parametrically estimate the cumulative incidence of experiencing a particular symptom, as an adjunct to the non-parametric Turnbull estimator, which was also presented. Presenting a parametric estimate was desirable as this allowed adjusting for covariates such as age, sex and admission to hospital, and providing confidence intervals.

Cure-mixture models were chosen because their assumptions were congruent with our knowledge of the disease process. Our data were poorly fit by classical parametric survival models, as these models explicitly assume that all patients eventually experience the symptom and attempt to fit the distribution of time using a parametric distribution. This assumption is known to be false when modeling discrete symptoms of a (often) self-limiting infectious disease, as patients who recover from their illness are no longer at risk of experiencing the symptom. By contrast, the cure-mixture models assume that the population is an unknown mixture of patients who are not at risk of experiencing the symptom, and that patients who are at risk will experience the symptom at a variable time from symptom onset. The model seeks to first estimate the proportion of susceptible patients and subsequently model their risk using a parametric distribution.

The data were collected during telehealth interviews. Patients were enrolled immediately after being found to be SARS-CoV-2-positive. Almost all patients underwent the enrollment interview within 24 hours of a positive test. During the first interview, patients were asked for the date when they first experienced symptoms, and were then asked whether they had experienced each of the 19 symptoms between the time of symptom onset and the time of the interview. The data were therefore interval censored, and this was taken into account during the modeling process. While some patients did test positive more than once, the latter tests were invariably performed due to a difficult discharge decision which included release from isolation. The result therefore had no bearing on the cumulative probability of experiencing a particular symptom, from symptom onset until discharge, and there was no need to account for this in our study.

4) Figure 1 I found was particularly useful. Some figures do need axis titles.

Reply:

We have updated the axis legends of all figures.

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