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Abstract

Background: COVID-19 has symptoms similar to several other respiratory and non-respiratory diseases, which makes differentiating them a challenging task and could lead to unnecessary use of realtime reverse transcriptase polymerase chain reaction (RT-PCR) resources.

Aims: The study aimed to assess self-reported symptoms as predictors for RT-PCR positivity in suspected COVID-19 cases.

Methods: This was a cross-sectional study. We retrospectively reviewed the database of COVID-19 care centres in the eastern district of Tripoli, Libya, from May to December 2020. Presenting symptoms and RT-PCR test data were extracted.

Results: Of the 4593 subjects, 923 (20.1%) had positive RT-PCR result. Sensitivity for COVID-19 disease diagnosis was very low (≤ 18.2%) for all symptoms, except for myalgia (82.1%). Specificity was high for all symptoms (90.7–99.8%), except for myalgia (11.0%). Loss of taste and smell had the highest positive likelihood ratio (LR) for RT-PCR positivity (LR+ = 3.59, 95% CI: 2.95–4.37). In the multiple logistic regression, three symptoms maintained significant contribution to RT-PCR positivity; these were loss of taste and smell (odds ratio (OR) = 3.90, 95% CI: 3.04–4.99), sore throat (OR = 1.50, 95% CI: 1.02–2.19), and myalgia (OR = 0.65, 95% CI: 0.49–0.85). Other significant predictors were history of contact with a COVID-19 case (OR = 0.50, 95% CI: 0.39–0.62), and being female (OR = 1.33, 95% CI: 1.15–1.55).

Conclusion: The findings of this study do not support the use of self-reported symptoms for the confirmation of COVID-19 disease in suspected cases because of their poor diagnostic properties.

Keywords: COVID-19, self-reported symptoms, predictors, sensitivity, specificity, respiratory disease, PCR

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Introduction

COVID-19 emerged at the end of 2019 in China, and by 7 January 2020, a novel type of coronavirus was identified (1,2). The disease then spread to other countries, and was declared a Global Health Emergency of International Concern on 30 January 2020 (2), and declared a pandemic on 11 March 2020 (3). The first case in Tripoli, Libya, where this study was conducted, was confirmed on 25 March 2020 (4). The pandemic has had adverse impacts on health (5,6), education and the economy (7,8), and constituted a major challenge to health care systems (9).

Early and accurate diagnosis of COVID-19 is important for disease management and control. The most accurate diagnostic test for the disease is the real-time reverse transcriptase-polymerase chain reaction (RT-PCR), which is based on the detection of the genetic material of the virus (10). However, the high global demand, and the shipment issues affected supplies to many countries. The shortage of RT-PCR resources is prominent in some developing countries, such as Libya, and has affected the early detection of COVID-19 cases. Besides RT-PCR, there are other tests with variable accuracy and complexity including antigen and antibody detection tests. Antigen rapid diagnostic tests are quick but less accurate than RT-PCR (11). They are more accurate in the first week of the development of symptoms (12),

particularly in cases with high viral load (13). Antibody detection tests have limited value in the first week of the infection because of their low sensitivity (10,14).

Researchers have evaluated the usefulness of symptoms in the identification of COVID-19 cases (15–21). Generally, the use of presenting symptoms in the prediction of a disease has been examined before, especially in respiratory diseases (22,23) or in diseases that have the same symptoms with respiratory diseases (24). In the context of epidemic infectious diseases, some studies have investigated the accuracy of symptoms for the diagnosis of severe acute respiratory syndrome (SARS) (25), and Ebola (26).

COVID-19 has the same symptoms with several respiratory infections like the common cold and influenza, and may present with nonrespiratory symptoms. This makes differentiation a challenging task, and can lead to unnecessary use of RT-PCR resources. Symptoms could be of value in guiding the decision about who is likely to have a positive RT-PCR, especially in settings where resources are limited, as in Libya, besides reducing the demand for RT-PCR.

Evidence from previous research on the accuracy of symptoms in distinguishing COVID-19 cases is inconsistent (27). Several studies were undertaken in hospitals (16,17) rather than in primary care settings, or among specific groups like health care workers (15,20,21) rather than in general public cohorts. Therefore, there is a need for further evaluation of the usefulness of symptoms for the diagnosis of COVID-19 (27).

In this study we examined self-reported symptoms as predictors of RT-PCR positivity in suspected COVID-19 cases.

Methods

Study design and settings

A cross-sectional study was conducted using the database of COVID-19 rapid response team at the COVID-19 care centres in the eastern district of Tripoli, Libya. The database was retrospectively reviewed from 1 May 2020 to 31 December 2020. The total number of recorded attendees with complete data was 4708. Of this total, 115 subjects were excluded based on the eligibility criteria of this study.

Study variables

The outcome variable, RT-PCR test status, was defined as a binary variable (positive, negative). It was based on the examination of nasopharyngeal swab specimens using RT-PCR. In addition to the presenting symptoms, data on age, sex, nationality and contact history were extracted. Both the sociodemographic data and the symptoms were self-reported.

Eligibility criteria

Based on literature relevant to children's survey methods (28–30), only the data for cases aged 8 years and older were included. Subjects with inconclusive RT-PCR results, which were coded as "repeat" in the database, were excluded.

Ethical considerations

Permission was obtained from the National Center of Disease Control (NCDC), Tripoli, Libya. Confidentiality was maintained as the data were anonymously coded.

Statistical analysis

We used SPSS, version 26, for statistical analysis. Frequency, percentage, mean and standard deviation were used to summarize the characteristics of the participants. The bivariate association between study variables and RT-PCR test status were assessed using the chi-squared test, Fisher's exact test and the independent t-test. Sensitivity, specificity, positive and negative predictive values and likelihood ratios were estimated to evaluate the diagnostic properties of each symptom. Variables that showed significant (P

Results

Sociodemographic characteristics and distribution of symptoms

Data for 4593 subjects with suspected COVID-19 were considered in the analysis (Table 1). Mean age was 38.2 (standard deviation 16.7) years, and males represented 54.7% of the sample. Overall, 94.9% were symptomatic and most presented with more than one symptom. The most frequently reported symptom was myalgia (88.0%); this was followed by fatigue, fever, cough and loss of taste and smell, but these were reported less frequently (Figure 1). A total of 16.2% reported other symptoms less frequently: headache (4.9%), dyspnoea (4.0%), sore throat (3.4%), runny nose (3.1%) and vomiting and diarrhoea (0.8%).

Unadjusted association between symptoms and RT-PCR positivity

Around 20.1% of the respondents suspected of having COVID-19 were confirmed positive with the RT-PCR (Table 2). A significantly greater proportion of females than males showed positivity (P

Validation of individual symptoms

Table 3 shows the diagnostic properties of each symptom. Sensitivity was very low for all symptoms (≤ 18.2%) except for myalgia (82.1%). However, specificity was high for all symptoms (90.7%–99.8%) except for myalgia (10.5%). All symptoms had a low positive predictive value (PPV) (≤ 47.4%), and the PPV of some symptoms like abdominal pain had wide 95% confidence interval (CI) indicating uncertainty. Loss of taste and smell had the highest positive likelihood ratio for RT-PCR positivity and thus for COVID-19 diagnosis (3.59, 95%CI: 2.95–4.37). All symptoms had negative likelihood ratio of 1 or close to 1.

Multivariate logistic regression analysis for RT-PCR positivity predictors

In the multivariate logistic regression analysis for the predictors of positive PCR test, 3 symptoms maintained significant contribution to PCR positivity in the controlled analysis (Table 4). These were loss of taste and smell, sore throat and myalgia. Other significant factors were sex and history of contact with a COVID-19 case.

Subjects who lost taste and smell were almost 4 times more likely to have a positive PCR than those who had not lost those senses [odds ratio (OR) = 3.90, 95% CI:3.04–4.99]. Subjects who reported having sore throat had 1.5 times greater odds of having a positive PCR than those who did not (OR = 1.50, 95% CI:1.02–2.19). Females were slightly more likely to have a positive test than males (OR = 1.33, 95% CI: 1.15–1.55).

Myalgia and history of contact with a COVID-19 case were negative predictors. Subjects who complained of myalgia had lower odds of having a positive test result than those who did not present with it (OR = 0.65, 95% CI: 0.49–0.85). Subjects who reported a history of contact had lower odds of RT-PCR positivity than those who had no contact history (OR = 0.50, 95% CI: 0.39–0.62).

This logistic regression model had very poor properties. Based on Nagelkerke's R2, it explains only 7.2% of the variation in having the PCR test positive. The overall accuracy is 79.9%, but it displayed a very low sensitivity (6.0%). The logistic regression model had a high specificity (98.4%), a low positive predictive value (PPV) (49.5%) and a moderate negative predictive value (NPV) (80.6%).

$Z = –0.700 + 1.362 \times$ Loss of taste and smell (Yes) $+ 0.694 \times$ Contact history (No) $+ 0.290 \times$ gender (Female) $– 0.424 \times$ Myalgia (Yes) $+ 0.406 \times$ Sore throat (Yes) Probability (positive PCR) $= 1/1 + ez$

= 1/1+e Z –0.700 + 1.362 × Loss of taste and smell (Yes) + 0.694 × Contact history (No) + 0.290 × gender (Female) – 0.424 × Myalgia (Yes) + 0.406 × Sore throat (Yes)

Discussion

A substantial proportion of the suspected cases were symptomatic, but the majority had presented with myalgia more often than with any other symptoms. Fatigue, fever, cough and loss of taste and smell were much less commonly presented. This symptom pattern differs in terms of frequency of symptoms and order of commonness from that reported in some other settings (18,20,21).

Initially, in the unadjusted analysis, 7 symptoms showed statistically significant association with RT-PCR status. Loss of taste and smell had the highest crude odds of RT-PCR positivity, with a 4-fold increase in the likelihood of the test being positive. As in our study, loss of taste showed the highest unadjusted odds of RT-PCR positivity among all studied symptoms in several other studies (20,21). We found that fever, cough and fatigue were associated with increased crude odds of test positivity, and this is consistent with other research (20). Sore throat was associated with an almost 2 times increase in the likelihood of having the infection. However, previous research findings on sore throat have been mixed; while some studies reported lower odds of having the disease in those who had a sore throat (20), others reported no difference unless the sore throat was combined with nasal symptoms (15), or even higher odds of PCR positivity in those who did not have sore throat (21). In our study, myalgia was associated with lower crude odds of test positivity, which is not consistent with the findings in some other studies (20,21).

With the exception of myalgia, all symptoms had very low sensitivity, but high specificity for detecting PCR positivity, and thus, for COVID-19 infection diagnosis. The high specificity of the symptom indicates that it correctly identifies subjects who do not have COVID-19 infection. That means those who do not have that symptom, generally do not have the infection. However, the very low sensitivity implies that sole reliance on any symptom for the diagnosis of COVID-19 would be associated with a high false-negative rate. In other words, many of the suspected subjects who actually have COVID-19 infection would not be identified. Consistent with our findings, a review of similar studies concluded that individual COVID-19 symptoms have very low sensitivity and moderate to high specificity (27). However, one study reported a relatively better sensitivity and a lower specificity for certain symptoms like loss of taste, sore throat and fever (19).

Subjects who had lost taste and smell were almost 4 times more likely to test positive than those who had not lost those senses. Several studies have reported loss of taste as one of the strongest predictors of PCR positivity (15,17–21). Sore throat showed a 1.5 times increase in the odds of having a positive RT-PCR, and this was in contrast to some studies (19,21).

Interestingly, myalgia maintained its contribution as a negative predictor in the controlled analysis, suspected cases who reported myalgia had lower odds of having a positive test result than those who did not report it. Myalgia is a subjective symptom, especially if measured via self-reporting, and this may partially explain this finding. The study did not control for comorbidity and a proportion of the reported myalgia may have been related to morbidities other than COVID-19. In contrast to our finding, some studies reported myalgia among the predictors of positive RT-PCR (15,19,21). As the respondents in those studies were either health care workers (15,21), or included a health care workers group (19), reporting of myalgia may have been more accurate than in our study.

History of contact with a COVID-19 case contributed significantly to the PCR test result as a protective factor, those who reported contact were less likely to be positive. In contrast to our findings, and in line with the theoretical expectations, a Hong Kong study found that contact history increased the likelihood of PCR positivity 10-fold (16). The reported protective contribution in our study may have been driven by some factors that were not controlled. Considering the Health Belief Model (31,32), we suggest that being aware of a positive contact nearby may increase the self-susceptibility perception and adherence to COVID-19 preventive behaviours. This could be one reason for the reported protective contribution. Another possible explanation is that the “no contact history” group may have included a proportion of subjects with “unknown positive contacts”. A proportion of those with “contact history” may have falsely tested negative as they presented early when they realized they had contacted a positive case, and thus were counted within the negative group.

This multiple regression model has a very low sensitivity, but a high specificity for diagnosis of COVID-19 infection. Although this regression model may be good at excluding those who do not have COVID-19 infection because of the high specificity, many of the subjects who have the infection will be missed if it is used. As in our study, some research has questioned the use of such models for the diagnosis of COVID-19 infection for their low sensitivity (23).

Several limitations should be considered in the interpretation of our findings. Most of these limitations are related to the nature of retrospective data collection. The subjective nature of self-reporting of symptoms, especially general nonrespiratory ones like myalgia and fatigue, may have affected measurement accuracy. Another weakness of the study is that it did not

control for co-morbidity due to the considerable amount of missing data on this variable in the database. Our study did not account for the time between the appearance of symptoms and performing the RT-PCR tests because this information was not available in the database. Thus, cases who had the RT-PCR test when they had just observed the symptoms may have been falsely included in the negative group due to the relatively higher false negativity of the test in the early stages of COVID-19.

However, the study does have its strengths. While several previous studies were undertaken in hospitals, or among specific groups like health care workers, which limits their external validity, this study used data from a relatively large cohort of the general public presenting in COVID-19 care centres, which is deemed to enhance the generalizability of its results.

Conclusions

Our findings agree with previous research on the importance of loss of taste and smell as a predictor of RT-PCR positivity. However, we do not support relying on symptoms alone for COVID-19 disease diagnosis in practice because of their overall poor diagnostic properties. Further research is recommended to assess the use of symptoms as predictors of RT-PCR positivity and to address our study limitations. In particular, we recommend considering a fixed time from the appearance of symptoms to taking the RT-PCR test for all subjects, which was not feasible in our study due to the limited availability of data and its retrospective nature. The current study was conducted when the original strain of SARS-COV-2 was dominant in Libya. Thus, further research is needed because the symptom pattern and the order in which symptoms appear vary between the original SARS-CoV-2 virus strain and other variants.

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Les symptômes auto-déclarés pourraient-ils constituer des facteurs prédictifs d'une positivité au test RT-PCR chez les cas suspects de COVID-19 ? L'expérience de la Libye

Résumé

Contexte : La COVID-19 présente des symptômes similaires à ceux de plusieurs autres maladies respiratoires et non respiratoires, ce qui rend leur différenciation difficile et pourrait entraîner un recours inutile aux ressources de l'amplification en chaîne par polymérase en temps réel (RT-PCR).

Objectifs : L'étude visait à évaluer les symptômes auto-déclarés en tant que facteurs prédictifs de la positivité au test RT-PCR chez les cas suspects de COVID-19.

Méthodes : Il s'agissait d'une étude transversale. Nous avons examiné rétrospectivement la base de données des centres de soins COVID-19 dans le district oriental de Tripoli en Libye, de mai à décembre 2020. Les symptômes qui se sont présentés et les données du test RT-PCR ont été extraits.

Résultats : Neuf cent vingt-trois sujets (20,1 %) sur 4593 présentaient un résultat positif à la RT-PCR. La sensibilité du diagnostic de la COVID-19 était très faible (≤ 18,2 %) pour tous les symptômes, à l'exception de la myalgie (82,1 %). La spécificité était élevée pour tous les symptômes (90,7-99,8 %), sauf pour la myalgie (11,0 %). La perte du goût et de l'odorat présentait le rapport de vraisemblance (RV) positif le plus élevé pour la positivité à la RT-PCR (RV+ = 3,59, IC à 95 % : 2,95-4,37). À la régression logistique multiple, trois symptômes ont maintenu une contribution significative à la positivité de la RT-PCR ; il s'agissait de la perte du goût et de l'odorat (OR = 3,90, IC à 95 % : 3,04-4,99), des maux de gorge (OR = 1,50, IC à 95 % : 1,02-2,19), et de la myalgie (OR = 0,65, IC à 95 % : 0,49-0,85). Les autres facteurs prédictifs significatifs étaient les contacts précédents avec un cas de COVID-19 (OR = 0,50, IC à 95 % : 0,39-0,62), et l'appartenance au sexe féminin (OR = 1,33, IC à 95 % : 1,15-1,55).

Conclusion : Les résultats de la présente étude ne soutiennent pas l'utilisation des symptômes auto-déclarés pour la confirmation de la présence de COVID-19 chez les cas suspects, en raison de leurs mauvaises propriétés diagnostiques.

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الملخص

الخلفية: أدى فيروس كورونا الجديد (COVID-19) المسبب لمتلازمة الجهاز التنفسي الحاد الوخيم 2 (SARS-CoV-2) إلى جائحة عالمية. تعد الأعراض المبلغ عنها ذاتيا من المرضى المشتبه بإصابتهم بالعدوى مؤشرا مهما لتشخيص العدوى. ومع ذلك، فإن الأعراض المبلغ عنها ذاتيا لا تتنبأ دائما بنتائج اختبار تفاعل البوليمراز المتسلسل بالنسخ العكسي (RT-PCR) الإيجابية.

الأهداف: تحديد الأعراض المبلغ عنها ذاتيا والتي تتنبأ بشكل أفضل بنتائج اختبار تفاعل البوليمراز المتسلسل بالنسخ العكسي (RT-PCR) الإيجابية لدى المرضى المشتبه بإصابتهم بعدوى COVID-19.

طرق البحث: تم إجراء دراسة مقطعية على المرضى المشتبه بإصابتهم بعدوى COVID-19 في مركز واحد للرعاية الثالثية في الرياض، المملكة العربية السعودية، من 1 مارس 2020 إلى 30 أبريل 2020. تم تحليل البيانات الديموغرافية والسريرية والمختبرية.

النتائج: من بين 4593 مريضا تم اختبارهم، كان 923 (20.1%) إيجابيين لفيروس SARS-CoV-2 بواسطة اختبار تفاعل البوليمراز المتسلسل بالنسخ العكسي (RT-PCR). كان الأشخاص الذين يعانون من فقدان حاسة الشم أو التذوق أكثر عرضة بمقدار 18.2 مرة (95% CI: 99.8% - 90.7) للإصابة بعدوى COVID-19 من أولئك الذين لا يعانون من هذه الأعراض. كان لدى 82.1% من المرضى الإيجابيين لفيروس SARS-CoV-2 حمى أو سعال أو ضيق في التنفس. كان لدى 11.0% فقط من المرضى الإيجابيين لفيروس SARS-CoV-2 إسهال. كان الأشخاص الذين يعانون من ألم في العضلات أكثر عرضة بمقدار 3.59 مرة للإصابة بعدوى COVID-19 (95% CI: 4.37–2.95). كان الأشخاص الذين يعانون من الصداع أكثر عرضة بمقدار 3.90 مرة للإصابة بعدوى COVID-19 (95% CI: 4.99-3.04). كان الأشخاص الذين يعانون من التهاب الحلق أقل عرضة بمقدار 1.50 مرة للإصابة بعدوى COVID-19 (95% CI: 2.19–1.02). كان الأشخاص الذين يعانون من الغثيان أو القيء أقل عرضة بمقدار 0.65 مرة للإصابة بعدوى COVID-19 (95% CI: 0.85–0.49). كان الأشخاص الذين يعانون من ضيق في التنفس أقل عرضة بمقدار 0.50 مرة للإصابة بعدوى COVID-19 (95% CI: 0.62–0.39). كان الأشخاص الذين يعانون من ألم في الصدر أكثر عرضة بمقدار 33.1 مرة للإصابة بعدوى COVID-19 (95% CI: 1.55–1.15).

الاستنتاجات: تشير نتائجنا إلى أن الأعراض المبلغ عنها ذاتيا يمكن أن تكون مؤشرا مهما لتشخيص عدوى COVID-19. ومع ذلك، فإن الأعراض المبلغ عنها ذاتيا لا تتنبأ دائما بنتائج اختبار تفاعل البوليمراز المتسلسل بالنسخ العكسي (RT-PCR) الإيجابية لعدوى COVID-19.

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