Challenges in interpreting the diagnostic performance of symptoms to predict COVID-19 status: The case of anosmia

There is mounting evidence that a sudden onset of altered sense of smell and/or taste is closely related to coronavirus disease-2019 (COVID-19). The severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) was observed to impair the sense of smell and/or taste in about two thirds of mild to moderate cases of COVID-19.\(^1,2\) Consequently, several studies have tried to estimate the sensitivity and specificity as well as the positive predictive value of self-reported new onset of smell and/or taste impairment for COVID-19 in populations of patients with flulike symptoms.

When faced with this task in the context of COVID-19, 2 main problems are predictably encountered. The first is that the standard diagnostic tool for diagnosis of SARS-CoV-2 infection, namely SARS-CoV-2 real-time polymerase chain reaction (RT-PCR) on a nasopharyngeal sample, is insufficient to rule-out COVID-19 when negative. Although its specificity is excellent, nasopharyngeal swab shows suboptimal sensitivity for SARS-CoV-2 detection in the early phase of infection being inconsistent during serial testing.\(^3\) Moreover, patients developing COVID-19–related symptoms may be referred to nasopharyngeal swab later during the course of the disease when viral load is no longer detectable.\(^4,5\) Thus, the diagnostic performance of new onset of smell and/or taste impairment for COVID-19 may be even higher than estimated. The other problem concerns the pretest probability of disease. Predictive values refer to the ability of a test result or symptom presence to confirm the presence or absence of a disease, based on positive predictive value (PPV) or negative predictive value (NPV), respectively. Although sensitivity and specificity are properties of a test itself that will not be affected by the characteristics and prevalence of disease in the population, PPV and NPV are strongly influenced by the prevalence of the disease in the target population.\(^6\) Among patients with flulike symptoms, the prevalence of SARS-CoV-2 infection may vary substantially according to geographic context and disease phase. For example, the study by Tostmann et al, conducted in The Netherlands during the early phase of the COVID-19 pandemic, demonstrated a prevalence of 11% in SARS-CoV-2–positive subjects among patients with a flulike illness,\(^7\) whereas Zayet et al reported a prevalence of 44% in their cohort of patients evaluated in a French hospital.\(^4\)

We performed a review of the literature to identify studies that tested patients with flulike symptoms for SARS-CoV-2 infection by RT-PCR and that reported data on the prevalence of loss of smell and/or taste. We identified a total of 6 studies (Fig. 1A).\(^2,4,7-10\) Sensitivity and specificity were represented using forest plots, and pooled estimates were calculated using a random intercept logistic regression model. Publication bias was assessed by funnel plot. PPVs and NPVs were calculated as a function of prevalence of COVID-19, ranging from 0% to 100%, using pooled sensitivity and specificity.

Forest plots of the sensitivity and specificity of new-onset chemosensory impairment for diagnosing COVID-19 are shown in Figure 1A. Although the pooled sensitivity was 61% (95% confidence interval [CI], 55-68%), pooled specificity reached 87% (95% CI, 80-92%), with publication bias being possible (Fig. 1B). Given this sensitivity and specificity, Figure 1C shows the variation of PPV and NPV, with a prevalence of SARS-CoV-2 infection in patients with flulike symptoms. For example, if the prevalence is 50%, PPV and NPV would be 82% and 69%, respectively; however, when prevalence is 10%, PPV would decline to 34% and NPV would increase to 95%.

Thus, in a different phase of the COVID-19 pandemic and in a different geographic context with a different diffusion of SARS-CoV-2, the PPV of the new onset of smell and/or taste loss may vary dramatically. Moreover, the increased impact of other viruses causing flulike symptoms may superimpose to SARS-CoV-2 circulation in next fall/winter season, thus further decreasing the PPV of new onset of smell and/or taste loss for COVID-19.

In conclusion, we believe that a new onset of smell and/or taste loss during the COVID-19 pandemic should be considered a manifestation of SARS-CoV-2 infection until proven otherwise, sufficient to justify testing, self-isolation, and the use of personal protective equipment by...
FIGURE 1. (A) Forest plot of sensitivity and specificity of alteration of sense of smell and/or taste in COVID-19. Each study’s sensitivity and specificity are presented as a black square, with size inversely proportional to standard error. The horizontal bar represents the 95% confidence interval. Rhombus represents the pooled sensitivity and specificity. (B) Funnel plot presents publication bias. (C) Simulation of positive and negative predictive values as a function of prevalence of COVID-19, calculated using pooled sensitivity and specificity. CI = confidence interval; COVID-19 = coronavirus disease-2019; Se = sensitivity; Sp = specificity.
medical personnel interacting with these subjects. However, taking into account the aforementioned considerations, diagnostic indications of individual symptoms should be fully understood and considered with caution when predicting SARS-CoV-2 infection in patients with flulike symptoms.

References

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