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

International Journal of Infectious Diseases 111 (2021) 37–42

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Prevalence of and factors associated with COVID-19 diagnosis in symptomatic patients followed in general practices in Germany between March 2020 and March 2021

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ARTICLE INFO

Article history:
Received 28 July 2021
Revised 4 August 2021
Accepted 5 August 2021

Keywords:
COVID-19 diagnosis
Prevalence
Associated factors
Symptomatic patients
General practices
Germany

ABSTRACT

Aims: This study aimed to investigate the prevalence of and the factors associated with the diagnosis of coronavirus disease 2019 (COVID-19) in symptomatic patients followed in general practices in Germany between March 2020 and March 2021.

Methods: Symptomatic patients tested for COVID-19 and followed in one of 962 general practices in Germany from March 2020 to March 2021 were included in this study. Covariates included sex, age, and comorbidities present in at least 3% of the population. The association between these factors and the diagnosis of COVID-19 was analyzed using an adjusted logistic regression model.

Results: A total of 301,290 patients tested for COVID-19 were included in this study (54.7% women; mean [SD] age 44.6 [18.5] years). The prevalence of COVID-19 was 13.8% in this sample. Male sex and older age were positively and significantly associated with COVID-19. In terms of comorbidities, the strongest positive associations with COVID-19 were observed for cardiac arrhythmias, depression, and obesity. There was also a negative relationship between the odds of being diagnosed with COVID-19 and several conditions such as chronic sinusitis, asthma, and anxiety disorders.

Conclusions: Approximately 14% of symptomatic patients tested for COVID-19 were diagnosed with COVID-19 in German general practices from March 2020 to March 2021.

Introduction

Coronavirus disease 2019 (COVID-19) refers to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a single-stranded RNA virus with predominant respiratory transmission (Baloch et al., 2020; Meyerowitz et al., 2020), which has triggered a worldwide and ongoing pandemic. As of 30 July 2021, more than 196 million people have contracted COVID-19, while the number of deaths has exceeded 4.2 million (World Health Organization, 2021). Despite the growing number of people being vaccinated against COVID-19, the weekly number of new cases in the world remains relatively high (e.g., more than 2.5 million cases per week in June and July 2021) (World Health Organization, 2021). Furthermore, multiple SARS-CoV-2 variants have been described (Gómez et al., 2021), and there is a significant risk of recurrent COVID-19 waves over the years ahead. In this context, further research is warranted to better understand the epidemiology of COVID-19.

In the past months, several studies have analyzed the prevalence of COVID-19 and the characteristics of people diagnosed with

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https://doi.org/10.1016/j.ijid.2021.08.010

this disease. The proportion of individuals diagnosed with COVID-19 has been found to vary widely between settings and countries (Elimian et al., 2020; Fan et al., 2020; Guerriero et al., 2021; Haimovich et al., 2020; Lusignan et al., 2020; Mani et al., 2020; Pouwels et al., 2021; Santos-Hövener et al., 2020; Shen et al., 2020; Shepard et al., 2021; Sundaram et al., 2021). For example, a retrospective study, including 24,081 healthcare workers who had nasopharyngeal swabs taken in an academic medical center in the United States between March and June 2020, showed that the prevalence of COVID-19 was around 0.59% (Shepard et al., 2021). By contrast, another cross-sectional study of 3,802 patients followed in primary care practices in the United Kingdom in January–April 2020 revealed that more than 15% of the sample had tested positive for SARS-CoV-2 (Lusignan et al., 2020). Despite the fact that these studies have advanced the field, most of them included participants irrespective of their potential symptomatology, and thus little is known about the specific prevalence of COVID-19 in those with common COVID-19 symptoms (e.g., cough, fatigue or fever). In terms of the sociodemographic and clinical characteristics of individuals diagnosed with COVID-19, the literature has also yielded some conflicting findings. For example, one study has found people with diabetes to be at an increased risk of COVID-19 compared to their counterparts without diabetes (Fan et al., 2020), while another has found that this is not the case (Lusignan et al., 2020). Taking these discrepancies into consideration, more data are needed on the rate of COVID-19 diagnosis among individuals with common COVID-19 symptoms, and on the sociodemographic and clinical characteristics of this population.

Therefore, the aim of this study was to investigate the prevalence of and the factors associated with COVID-19 diagnosis in symptomatic patients tested for COVID-19 and followed in general practices in Germany between March 2020 and March 2021.

Methods

Database

This retrospective study used data from the Disease Analyzer database (IQVIA), a database containing demographic, clinical, biological, and pharmaceutical data obtained in primary care practices (Rathmann et al., 2018). These data are collected in an anonymous format from general and specialized practices. Diagnoses are coded using the German version of the International Classification of Diseases, 10th revision (ICD-10), and prescriptions using the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Marketing Research Association (EphMRA). The quality of the data available in the database is regularly assessed on the basis of several criteria such as completeness of documentation and linkage between clinical and pharmaceutical data (Rathmann et al., 2018). The Disease Analyzer database contains data from around 3% of all general and specialized practices in Germany. Multiple characteristics (i.e., age of physician, specialty, community size category, and German federal state) are used to select practices for inclusion in the database. Finally, previous research has shown that this database is representative of all outpatient practices in Germany (Rathmann et al., 2018).

Study population

This study included all patients aged ≥14 years displaying COVID-19-like symptoms who were tested for COVID-19 and followed in one of 962 general practices in Germany between March 2020 and March 2021. The index date corresponded to the date on which the COVID-19 test was documented. If multiple COVID-19 tests were performed for the same individual, the index date corresponded to the first test.

COVID-19 diagnosis

COVID-19 diagnosis relied on two ICD-10 codes: U07.1 (COVID-19, virus identified) and U07.2 (COVID-19, virus not identified).

Study covariates

Study covariates included sex, age, and a number of conditions documented in at least 3% of the sample within 12 months prior to the index date. These conditions were: hypertension (ICD-10: I10); thyroid gland disorders (ICD-10: E00-E07); depression (ICD-10: F32 and F33); gastritis and duodenitis (ICD-10: K29); dermatitis and eczema (ICD-10: L20-L30); lipid metabolism disorders (ICD-10: E78); somatoform disorders (ICD-10: F45); reaction to severe stress, and adjustment disorders (ICD-10: F43); chronic sinusitis (ICD-10: J32); osteoarthritis (ICD-10: M15-M19); sleep disorders (ICD-10: F51 and G47); reflux diseases (ICD-10: K20-K22); chronic headache (ICD-10: G43 and G44); asthma (ICD-10: J45 and J46); diabetes mellitus (ICD-10: E10-E14); obesity (ICD-10: E66); phlebitis and thrombosis (ICD-10: I80-I84); allergic rhinitis (ICD-10: J30); anxiety disorders (ICD-10: F41); cardiac arrhythmias (ICD-10: I46-I49); noninfective enteritis and colitis (ICD-10: K50-K52); chronic obstructive pulmonary disease (COPD; ICD-10: J44); spondylosis (ICD-10: M47); vitamin D deficiency (ICD-10: E55); mononeuropathies (ICD-10: G56-G59); cancer (ICD-10: C00-C97); and iron deficiency anemia (ICD-10: D50).

Statistical analyses

The demographic and clinical characteristics of the study population were analyzed. The prevalence of COVID-19 was also estimated by dividing the number of people diagnosed with COVID-19 by the number of symptomatic patients tested for COVID-19. Finally, the relationship between demographic and clinical variables and COVID-19 diagnosis was studied using a logistic regression model. This logistic regression model included COVID-19 diagnosis as the dependent variable, and sex, age, and all conditions mentioned above as the independent variables. The results of the regression analysis are displayed as odds ratios (ORs) and 95% confidence intervals (CIs). P-values lower than 0.05 were considered statistically significant. Analyses were performed using SAS 9.4 and R 4.1.0 (R Core Team, 2021).

Results

This study included 301,290 symptomatic patients tested for COVID-19 and followed in 962 general practices. Of these, 54.7% were women and the mean (standard deviation) age was 44.6 (18.5) years (Table 1). The three most common conditions were hypertension (16.4%), thyroid gland disorders (12.3%), and depression (12.0%). The prevalence of COVID-19 was 13.8% in the overall sample. The results of the adjusted logistic regression analysis are displayed in Figure 1. COVID-19 diagnosis was positively and significantly associated with male sex (OR 1.04, 95% CI: 1.02-1.06) and older age (reference: 14-25 years; ORs ranging from 1.07 [95% CI: 1.03-1.11] in the age group 26-35 years to 1.80 [95% CI: 1.73-1.88] in the age group >65 years). In terms of comorbidities, there was a positive and significant relationship between COVID-19 diagnosis and cardiac arrhythmias (OR 1.33, 95% CI: 1.26-1.39); depression (OR 1.18, 95% CI: 1.14-1.23); obesity (OR 1.17, 95% CI: 1.12-1.23); iron deficiency anemia (OR 1.11, 95% CI: 1.05-1.18); diabetes mellitus (OR 1.10, 95% CI: 1.05-1.15); phlebitis and thrombosis (OR 1.06, 95% CI: 1.01-1.11); gastritis and duodenitis (OR 1.05, 95% CI: 1.01-1.09); osteoarthritis (OR 1.05, 95% CI: 1.01-1.09); and hypertension (OR 1.04, 95% CI: 1.00-1.07). By contrast, factors negatively and significantly associated with the odds of being diagnosed with

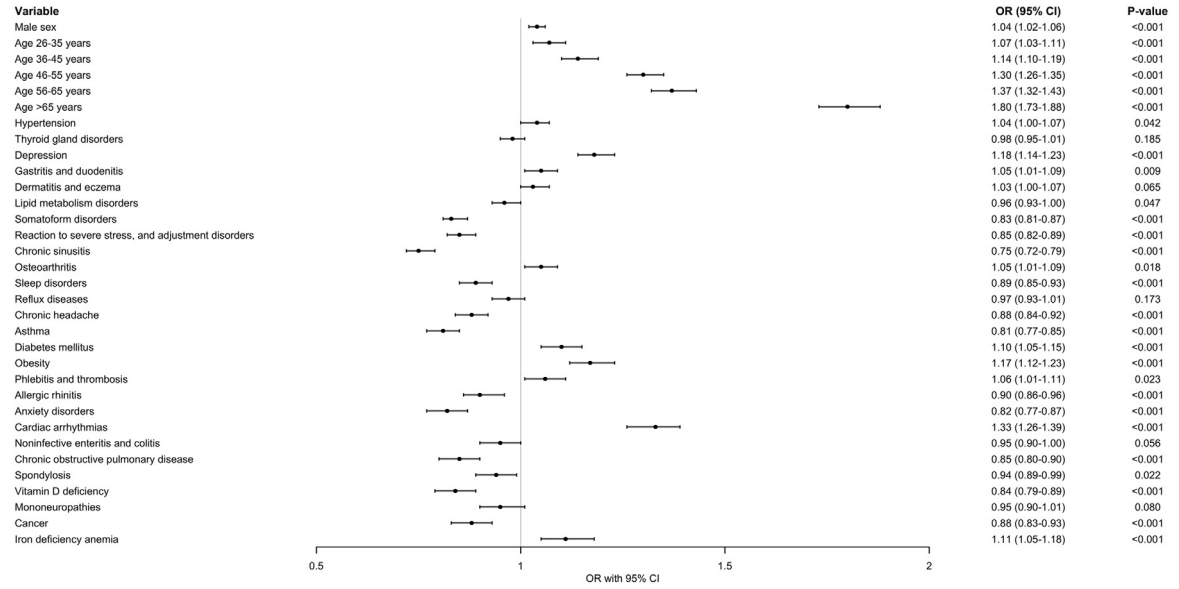

Figure 1. Relationship between demographic and clinical variables and COVID-19 diagnosis in symptomatic patients tested for COVID-19 and followed in general practices in Germany between March 2020 and March 2021.
Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; OR = odds ratio.
Female sex and age 14-25 years were the reference group for sex and age, respectively.
The adjusted logistic regression model included all demographic and clinical variables displayed in the figure.

Table 1
Demographic and clinical characteristics of the study population (N = 301,290).

Variable	Value
Sex	
Female	54.7
Male	45.3
Age (in years)	
Mean (standard deviation)	44.6 (18.5)
14-25	17.4
26-35	19.1
36-45	18.0
46-55	17.8
56-65	15.0
>65	12.8
Disorders diagnosed within 12 months prior to the index date	
Hypertension	16.4
Thyroid gland disorders	12.3
Depression	12.0
Gastritis and duodenitis	11.4
Dermatitis and eczema	10.7
Lipid metabolism disorders	10.2
Somatoform disorders	9.3
Reaction to severe stress, and adjustment disorders	8.1
Chronic sinusitis	8.0
Osteoarthritis	7.9
Sleep disorders	7.8
Reflux diseases	7.1
Chronic headache	6.4
Asthma	6.0
Diabetes mellitus	5.9
Obesity	5.5
Phlebitis and thrombosis	4.9
Allergic rhinitis	4.8
Anxiety disorders	4.7
Cardiac arrhythmias	4.7
Noninfective enteritis and colitis	4.4
Chronic obstructive pulmonary disease	4.2
Spondylosis	4.1
Vitamin D deficiency	4.1
Mononeuropathies	3.8
Cancer	3.3
Iron deficiency anemia	3.2

Abbreviation: COVID-19 = coronavirus disease 2019.
Data are indicated in percentages unless otherwise specified.

COVID-19 included chronic sinusitis (OR 0.75, 95% CI: 0.72-0.79); asthma (OR 0.81, 95% CI: 0.77-0.85); anxiety disorders (OR 0.82, 95% CI: 0.77-0.87); somatoform disorders (OR 0.83, 95% CI: 0.81-0.87); vitamin D deficiency (OR 0.84, 95% CI: 0.79-0.89); COPD (OR 0.85, 95% CI: 0.80-0.90); reaction to severe stress, and adjustment disorders (OR 0.85, 95% CI: 0.82-0.89); cancer (OR 0.88, 95% CI: 0.83-0.93); chronic headache (OR 0.88, 95% CI: 0.84-0.92); sleep disorders (OR 0.89, 95% CI: 0.85-0.93); allergic rhinitis (OR 0.90, 95% CI: 0.86-0.96); spondylosis (OR 0.94, 95% CI: 0.89-0.99); and lipid metabolism disorders (OR 0.96, 95% CI: 0.93-1.00).

Discussion

Main findings

This retrospective study, including approximately 301,300 symptomatic patients tested for COVID-19 and followed in more than 960 general practices in Germany between March 2020 and March 2021, revealed that the prevalence of COVID-19 was around 14% in the sample. The adjusted regression analysis also found that male and older patients were more likely to be diagnosed with COVID-19 than female and younger patients. COVID-19 was also positively associated with several conditions, and the OR of these associations was the highest for cardiac arrhythmias, depression, and obesity. By contrast, negative relationships were observed between COVID-19 diagnosis and multiple comorbidities such as chronic sinusitis, asthma, and anxiety disorders. It is believed that this is among the largest studies to have investigated the prevalence of and the factors associated with COVID-19 diagnosis in primary care practices.

Interpretation of the findings

This German study showed that slightly less than one in seven symptomatic patients tested for COVID-19 was actually diagnosed with COVID-19. It is difficult to compare this finding with the findings of previous studies, as most of these studies included symptomatic and asymptomatic participants and were conducted

in other settings and countries. That being said, a U.S. study of 3,477 symptomatic healthcare workers reported that 5.3% of the sample had COVID-19 (Mani et al., 2020). Another study using data from 2,203 individuals from Germany collected in May–June 2020 found that none of the throat swabs taken was positive for SARS-CoV-2 (Santos-Hövener et al., 2020). Based on these results, the prevalence of COVID-19 reported in the present study appears to be relatively high. This finding underlines the major role played by general practices in the diagnosis of COVID-19 in Germany and also reinforces the importance of preventive measures in controlling the transmission of the virus between patients of the same practice in this country (Eisele et al., 2021).

The second aim of the present study was to identify demographic and clinical factors that were significantly associated with the odds of being diagnosed with COVID-19. Interestingly, in line with previous research (Fan et al., 2020; Lusignan et al., 2020), there was a positive association between male sex, older age, and COVID-19 diagnosis. Although the strength of the association between sex and the diagnosis of COVID-19 was relatively weak (i.e., OR 1.04), this association could potentially result in a difference of hundreds of thousands of COVID-19 positive cases between men and women at the population level. There are major sex-related differences in the human physiological response against SARS-CoV-2 at various stages of the infection (e.g., virus entry, virus sensing, and innate immune response), and these differences may result in a higher risk of COVID-19 or more persistent detection of viral RNA in men than in women (Scully et al., 2020; Xu et al., 2020). From a behavioral perspective, previous research has also shown that compliance with preventive public measures is lower in men than in women (Galasso et al., 2020), which may at least partially explain the relationship between sex and COVID-19 diagnosis observed in this study. Finally, several age-related changes such as immunosenescence, inflammation, and a dysregulated renin-angiotensin system may increase COVID-19 susceptibility in older adults compared to their younger counterparts (Mueller et al., 2020).

In terms of comorbidities, COVID-19 diagnosis was strongly and positively associated with cardiac arrhythmias, depression, and obesity. A substantial body of literature has suggested that cardiac arrhythmias are relatively common in people with COVID-19 (Cho et al., 2020; Gopinathannair et al., 2020; Rav-Acha et al., 2021). One study of 390 hospitalized COVID-19 patients from Israel showed that 7.2% of them had arrhythmias (e.g., tachyarrhythmias or bradyarrhythmias) (Rav-Acha et al., 2021). Although cardiac arrhythmias were documented prior to the diagnosis of COVID-19 in this study conducted in Germany, it is possible that patients were already infected with SARS-CoV-2 when diagnosed with cardiac arrhythmias. With regard to mental health, previous literature has also identified depression as a risk factor for COVID-19, and the association between depression and COVID-19 could be mediated by factors such as difficulties in complying with preventive measures and limited access to healthcare (Wang et al., 2021). Finally, the current study found that people with obesity were more likely to have COVID-19 than those without obesity, and this result is in line with previous data. As a matter of fact, a meta-analysis of 50 studies (N = 18,260,378 participants) found a positive relationship between obesity and SARS-CoV-2 infection and severe COVID-19 symptoms (Yang et al., 2020). Given that adipose tissues express the angiotensin-converting enzyme 2 (ACE2) (Al-Benna, 2020), a receptor that plays a key role in the cellular entry of SARS-CoV-2 (Ziegler et al., 2020), excess adiposity may increase the risk of COVID-19 diagnosis. Furthermore, there is strong evidence highlighting the negative impact of obesity on the immune response to infection (Milner and Beck, 2012).

By contrast, this study found relatively strong negative associations between chronic sinusitis, asthma, and COVID-19. As previous research has obtained different findings in this regard, these relationships should be interpreted with caution. For example, in a case-control study of 54 patients in a hospital setting in Spain, chronic rhinosinusitis was significantly associated with prolonged SARS-CoV-2 RNA shedding (Recalde-Zamacona et al., 2021). Regarding asthma, a systematic review and meta-analysis of 131 studies (N = 410,382 patients) identified a substantial degree of variability in the prevalence of asthma among those diagnosed with COVID-19 (the prevalence ranged from 1.1% to 16.9%), while there was no significant difference in this prevalence with respect to COVID-19 severity (Liu et al., 2021). That being said, there is an overlap in the symptoms of COVID-19, asthma, and chronic sinusitis, and, for example, the prevalence of COVID-19 has been found to be significantly lower in asthma patients with suspected COVID-19 than in their counterparts without asthma (Cao et al., 2021). Moreover, as fear of being diagnosed with COVID-19 is relatively common in individuals with asthma or other conditions affecting the airway (de Boer et al., 2021; Mousing and Sørensen, 2021), adherence to preventive measures may be higher in these individuals than in the general population. A cross-sectional study including 2,372 young adults from Mexico indicated that adherence to guidelines aimed at preventing the spread of COVID-19 was significantly higher in those with asthma (69.2%) than in those without asthma (43.8%) (Vázquez-Nava et al., 2020). Finally, the present German study found a negative relationship between anxiety disorders and COVID-19 diagnosis. Although psychiatric disorders are associated with an increased risk of COVID-19 (Taquet et al., 2021), less is known about the specific effects of pre-existing anxiety disorders on the incidence of SARS-CoV-2 infection, and some data suggest that compliance with preventive measures is higher when anxiety is present (Apisarnthanarak et al., 2020; Mevorach et al., 2021). These data could explain why patients with anxiety disorders had lower odds of being diagnosed with COVID-19 than those without anxiety disorders in the present German study.

Public health implications and directions for future research

The results of the present study conducted in Germany showed that around 14% of symptomatic patients who were tested for COVID-19 were diagnosed with the disease. Given that slightly less than one out of five patients diagnosed with COVID-19 will develop a severe form of the disease (Hu et al., 2020), it is of particular importance to follow up on COVID-19 patients on a regular basis and to avoid any potential delay in the referral of those with severe COVID-19 symptoms to emergency departments. In addition, as individuals with COVID-19 are likely to be infectious for up to 10 days following the onset of symptoms (Walsh et al., 2020), general practitioners should promote self-isolation at home and ensure that contact is limited among household members. Finally, healthcare providers should bear in mind that several conditions such as cardiac arrhythmias, depression, and obesity may be risk factors for or correlates of symptomatic COVID-19. In terms of future research, further studies are needed to analyze the prevalence of COVID-19 in primary care practices in more detail, while additional data of a longitudinal nature are required to better identify factors significantly associated with SARS-CoV-2 infection.

Strengths and limitations

The major strengths of this study are the large sample size and the use of data obtained in more than 960 general practices. However, the study results should be interpreted in the light of several limitations. First, no COVID-19-like symptoms were documented in the database, and it was therefore not possible to assess the prevalence of specific symptoms (e.g., cough, fatigue, or fever) in the sample and their individual association with COVID-19 diagnosis.

Second, there was a lack of data on health behaviors (e.g., physical activity or adherence to preventive measures), although these behaviors may predict the risk of being diagnosed with COVID-19. Third, a substantial proportion of patients with COVID-19 may have been diagnosed in emergency departments, and the prevalence of COVID-19 may thus have been underestimated in the present study. Furthermore, people at a particular risk of developing severe COVID-19 (e.g., those with obesity or COPD) may have been followed in specialized practices, potentially biasing the estimates obtained on the basis of the logistic regression analysis.

Conclusions

This study, which included around 301,300 symptomatic patients tested for COVID-19 and followed in general practices in Germany between March 2020 and March 2021, found that approximatively 14% of the patients were diagnosed with COVID-19. Male sex, older age, and several comorbidities (e.g., cardiac arrhythmias, depression, and obesity) were significantly and positively associated with COVID-19, while there was also a negative relationship between a wide range of conditions (e.g., chronic sinusitis, asthma, and anxiety disorders) and the diagnosis of COVID-19. Further longitudinal studies are needed to confirm or refute the results of this study.

Conflicts of interest: The authors declare that they have no competing financial interests.

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

Author contributions: Louis Jacob contributed to the design of the study, managed the literature searches, wrote the first draft of the manuscript, and corrected the manuscript. Ai Koyanagi, Lee Smith, Josep Maria Haro, and Anna M. Rohe corrected the manuscript. Karel Kostev contributed to the design of the study, performed the statistical analyses, and corrected the manuscript. All authors contributed to and have approved the final manuscript.

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