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Short communication

Do not neglect SARS-CoV-2 hospitalization and fatality risks in the middle-aged adult population

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ABSTRACT

Objectives: This study aimed at estimating the SARS-CoV-2 infection hospitalization (IHR) and infection fatality ratios (IFR) in France.
Patients and methods: A serosurvey was conducted in 9782 subjects from the two French regions with the highest incidence of COVID-19 during the first wave of the pandemic and coupled with surveillance data.
Results: IHR and IFR were 2.7% and 0.49% overall. Both were higher in men and increased exponentially with age. The relative risks of hospitalization and death were 2.1 (95% CI: 1.9-2.3) and 3.8 (2.4-4.2) per 10-year increase, meaning that IHR and IFR approximately doubled every 10 and 5 years, respectively. They were dramatically high in the very elderly (80-90 years: IHR: 26%, IFR: 9.2%), and also substantial in younger adults (40-50 years: IHR: 0.98%, IFR: 0.042%).
Conclusions: These findings support the need for comprehensive preventive measures to help reduce the spread of the virus, even in young or middle-aged adults.

1. Introduction

The SARS-CoV-2 infection hospitalization ratio (IHR, probability of hospitalization in infected individuals) and the infection fatality ratio (IFR, probability of death in infected individuals) are critical parameters in public health decision-making regarding the prioritization of control measures. However, age- and sex-related estimates are scarce, as they require reliable cumulative estimates of past infections, hospitalizations and deaths. By May 11, 2020, the cumulative number of COVID-19-related hospitalizations and hospital deaths in France had reached 96,000 and 17,000, respectively. At that time, knowledge was still limited regarding therapeutics likely to improve survival (anticoagulants, corticosteroids, high-flow nasal oxygen). This study estimated the age- and sex-specific IFR and IHR in France for this period based on contemporary SARS-CoV-2 seroprevalence data.

2. Materials and methods

Data from a seroprevalence study performed in May-June 2020 in 20-to 90-year old subjects were used. This study included subjects from three pre-existing general adult population cohorts from Île-de-France ($N = 6348$) and Grand Est ($N = 3434$), the two regions of France with the highest incidence of COVID-19 during the first wave of the pandemic [1]. All participants from these cohorts with regular access to online questionnaires were invited to participate

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in the study, and dried-blood spots were collected in random sampling among them.

In all participants, an EuroImmun IgG test against the S1 domain of the spike protein (Elisa-S1) was performed. When the Elisa-S1 optical density ratio was ≥0.7, two further tests (EuroImmun IgG test against Nucleocapsid protein and an in-house micro-neutralization assay to detect neutralizing anti-SARS-CoV2 antibodies) were performed. We assumed that participants with at least one positive test and no negative test were truly infected. Among the participants assumed truly infected, 82% (278/338) had three positive tests, 15% (52/338) had two positive tests and 2% (8/338) had one positive test. Since specificity was higher than 95% for each test independently (it was 100% for the neutralization assay [2]), the likelihood of two or three false positive tests in uninfected individuals could be considered negligible and the likelihood of one false positive test in uninfected individuals was very low and concerned very few participants. We therefore assumed specificity to be 100%. However, in this imputation model, an Elisa-S1 < 0.7 was sufficient for a patient to be classified as non-infected, which may have been biased by the imperfect sensitivity of this serological method. We estimated the sensitivity of Elisa-S1 at this threshold (0.7) in participants in the cohort with positive RT-PCR result. We found that 91 participants had positive SARS-CoV-2 RT-PCR less than 3 months before the serological test, among whom 76 presented with Elisa-S1 ≥ 0.7, suggesting Elisa-S1 test sensitivity at this threshold of 84% (75%, 90%). This value was in line with the sensitivity reported at a threshold of 0.8 in an evaluation performed in SARS-CoV-2 PCR+ confirmed plasma donors (90.4% [84.4%, 94.7%]) [3]. To account for the imperfect sensitivity of the serological tests, we assumed 85% sensitivity in our analyses. Sensitivity analyses were conducted around this parameter, with sensitivities ranging from 80% to 100%. Multiple imputation using (log-transformed) numerical values from the three serological tests, region, age and sex was used to infer the probability of infection among participants who could not be classified as either infected or uninfected (Elisa-S1≥ 0.7 and at least one negative test).

Seroprevalence estimates were calibrated by generalized raking in relation to census data from the general adult population, excluding nursing home residents who were not part of the cohort target population. The cumulative numbers of hospital admissions and deaths ascribable to COVID-19 were obtained from the SI-VIC database, the exhaustive national inpatient surveillance system used during the pandemic. Patients from nursing homes were removed from these counts. Since the median date of sample collection in the serosurvey was May 14, hospital admissions and deaths were considered up to May 6 and May 13 to account for estimated 11- and 19- day time lapses from infection to hospitalization and seroconversion, respectively [4,5], and an estimated 7-day time lapse from hospitalization to death (SI-VIC data [6]). We report IHR and IFR by sex and 10-year age class. Multivariable random-effect meta-regression models were fitted to estimate the relative risks (RR) of hospitalization and death according to age and sex, using age class as a continuous covariate.

3. Results

Assuming 85% sensitivity for the serological tests, overall estimated IHR and IFR in the French adult population (excluding nursing homes) were 2.7% (95% CI: 2.4, 3.0) and 0.49% (95% CI: 0.44, 0.56), respectively. We found a strong log-linear relationship between age and the risk of hospitalization or death, corresponding to an exponential increase in risk with age (Fig. 1). Estimated IHR in 20-30, 40-50, 60-70 and 80-90-year-old subjects were 0.39% (95% CI: 0.26, 0.61), 0.98% (95% CI: 0.82, 1.2), 5.9% (95% CI: 4.5, 7.6) and 26% (95% CI: 8.5, 84), respectively (RR: 2.1 (95% CI: 1.9, 2.3) per 10-year increase). Estimated IFR in these same age groups were 0.0065% (95% CI: 0.0043, 0.010), 0.042% (95% CI: 0.035, 0.051), 0.89 (95% CI: 0.68, 1.2) and 9.2% (95% CI: 3.0, 30), respectively (RR: 3.8 (95% CI: 2.4, 4.2) per 10-year increase). Both IHR and IFR were higher in men than in women for all age classes: RR 1.5 (95% CI: 1.1, 2.1) and 2.5 (95% CI: 1.8, 3.5), respectively. IHR and IFR estimates for sensitivities ranging from 80% to 100% are reported in Online supplements, respectively. These estimates are directly proportional to the assumed sensitivities, which does not impact their order of magnitude.

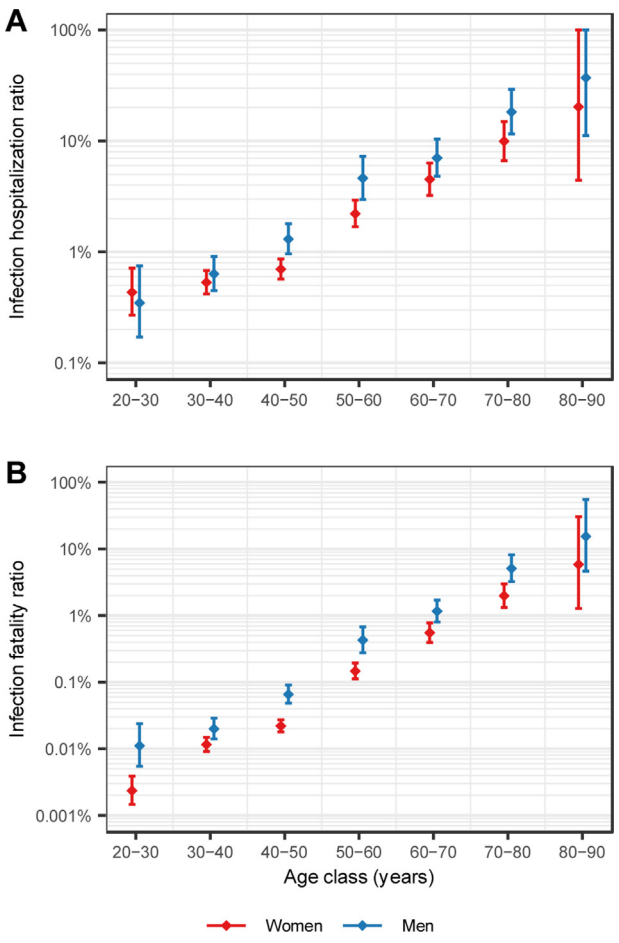

Fig. 1. Infection hospitalization ratio and infection fatality ratio with 95% confidence intervals by sex and age class: A. Infection hospitalization ratio. B. Infection fatality ratio.

4. Discussion

We estimated overall IHR of 2.7% and IFR of 0.49% in the adult population, excluding patients in nursing homes. Though these ratios may be underestimated in the elderly (nursing home residents are likely to experience poorer outcomes), our estimates are in line with earlier models [5] and various age-specific IFR estimates, worldwide [7]. IFR exponentially increases with age (doubling every 5.2 years) and is higher in men. While both IHR and IFR were dramatically elevated in the very elderly, this should not obscure substantial estimates in the young or middle-aged adult population. For example, in 20- to 30-year-old adults, the risk of death is 5 to 10 times that of a skydiving jump (1 per 100,000 jumps [8]) and in 40 to 50-year-olds, this risk of death is close to that of a BASE jump (1 to 2 per 1000 jumps [8]). As a comparison with another pandemic respiratory disease, the IFR estimates for

SARS-CoV-2 are approximately 100 times as high as those for influenza A(H1N1pdm09) (1 to 10 deaths per 100,000 infections) [9]. From a public health perspective, and even though substantial therapeutic improvements have certainly improved survival since the data for this study were collected, our findings underline the need for comprehensive preventive measures to help reduce the spread of the virus, even in young or middle-aged adults.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

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Authors' contributions

Conceptualization: SC and FC; methodology: NL, JP, SC and FC; formal analysis: NL and JP; resources: DLB, XdL, GS, MT, MZ, SC and FC; writing-original draft preparation: NL; writing-review and editing: all authors; supervision and project administration: SC and FC; funding acquisition: FC. All authors have read and agreed to the published version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. The SAPRIS-SERO study group

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.idnow.2020.12.007.

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