MEDICINA CLINICA

ELSEVIER

Original article

Susceptibility and risk of SARS-COV-2 infection among middle-aged and older adults in Tarragona area, Spain

Eva M. Satué-Gracia [a,b,*], Angel Vila-Córcoles [a,b], Cinta de Diego-Cabanes [c], Angel Vila-Rovira [b], Cristina Torrente-Fraga [d], Frederic Gómez-Bertomeu [e], Imma Hospital-Guardiola [f], Olga Ochoa-Gondar [b,g], Francisco Martín-Luján [a,b]

[a] Primary Care Department Camp de Tarragona, Institut Català de la Salut (ICS), Unitat de Suport a la Recerca (USR), Camí de Riudoms, 53-55, 43202 Reus (Tarragona), Spain
[b] Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAP J Gol), Gran Via Corts Catalanes, 587, 08007 Barcelona, Spain
[c] Primary Care Department Camp de Tarragona, Institut Català de la Salut (ICS), Centre d'Alta Resolució (CAR) Salou, Tarragona, Spain
[d] Technology and Informatic Department Camp de Tarragona, Institut Català de la Salut (ICS), Tarragona, Spain
[e] Universitary Hospital Joan XXIII, Institut Català de la Salut (ICS), Microbiology Department, Tarragona, Spain
[f] Primary Care Department Camp de Tarragona, Institut Catala de la Salut (ICS), Centre d'Atenció Primària (CAP) Dr. Sarró-Valls Urbà, Tarragona, Spain
[g] Primary Care Department Camp de Tarragona, Institut Català de la Salut (ICS), Centre d'Atenció Primària (CAP), Sant Pere i Sant Pau-Tarragona 5, Tarragona, Spain

ARTICLE INFO

ABSTRACT

Objective: To analyse susceptibility/risk of suffering COVID-19 among adults with distinct underlying medical conditions.

Methods: Population-based cohort study involving 79,083 individuals ≥50 years old in Tarragona (Southern Catalonia, Spain). Baseline cohort characteristics (demographic, pre-existing comorbidities, chronic medications and vaccinations history) were established at study start (01/03/2020) and primary outcome was laboratory-confirmed COVID-19 occurred among cohort members throughout 01/03/2020–30/06/2020. Risk of suffering COVID-19 was evaluated by Cox regression, estimating multivariable hazard ratios (HRs) adjusted for age/sex and pre-existing comorbidities.

Results: Across study period, 536 laboratory-confirmed COVID-19 cases were observed (mean incidence: 39.5 cases per 100,000 persons-week). In multivariable-analysis, increasing age/years (HR: 1.01; 95% CI: 1.00–1.02), nursing-home (HR: 20.19; 95% CI: 15.98–25.51), neurological disease (HR: 1.35; 95% CI: 1.03–1.77), taking diuretics (HR: 1.39; 95% CI: 1.10–1.75), antiplatelet (HR: 1.36; 95% CI: 1.05–1.76) and benzodiazepines (HR: 1.24; 95% CI: 1.00–1.53) increased risk; conversely, taking angiotensin-converting-enzyme inhibitors (HR: 0.78; 95% CI: 0.61–1.00), angiotensin-receptor-blockers (HR: 0.70; 95%CI: 0.51–0.96) and statins (HR: 0.75; 95% CI: 0.58–0.96) were associated with reduced risk. Among community-dwelling individuals, pre-existing cancer, renal and cardiac disease appeared also related with an increased risk, whereas influenza vaccination was associated with reduced risk.

Conclusion: In a setting with relatively low incidence of COVID-19 across the first wave of pandemic period, increasing age, nursing-home residence and multiple comorbidities appear predisposing for COVID-19 among middle-aged/older adults. Conversely, statins, angiotensin-receptor blockers/inhibitors and influenza vaccination were related with decreased risk.

* Corresponding author.
E-mail address: esatue.tgn.ics@gencat.cat (E.M. Satué-Gracia).

Susceptibilidad y riesgo de infección por SARS-CoV-2 en adultos mayores de 50 años en el área de Tarragona

R E S U M E N

Palabras clave:
Coronavirus
SARS-CoV-2
COVID-19
Incidencia
Riesgo

Objetivo: Analizar incidencia y riesgo/susceptibilidad de sufrir la COVID-19 en adultos según distintas condiciones médicas preexistentes.

Métodos: Cohorte de base poblacional que incluyó 79.083 personas ≥50 años en Tarragona. Características basales de la cohorte (edad/sexo, comorbilidades, medicaciones crónicas) se establecieron a 01-03-2020 y se registraron todos los casos de COVID-19 confirmada ocurridos en miembros de la cohorte hasta el 30-06-2020. Para estimación de riesgos se realizó regresión de Cox, con cálculo de hazard ratio (HR) ajustados por edad, sexo y comorbilidad.

Resultados: Se observaron 536 casos confirmados de COVID-19 (incidencia media: 39,5 casos por 100.000 personas-semana). En análisis multivariante, edad/años (HR: 1,01; IC el 95%: 1,00-1,02; p = 0,050), estar institucionalizado/residencia (HR: 20,19; IC 95%: 15,98-25,51; p<0,001), enfermedad neurológica (HR: 1,35; IC el 95%: 1,03-1,77), diuréticos (HR: 1,39; IC 95%: 1,10-1,75), antiagregantes plaquetarios (HR: 1,36; IC 95%: 1,05-1,76) y benzodiacepinas (HR: 1,24; IC 95%: 1,00-1,53) se asociaron con un riesgo aumentado de la COVID-19 analizando la totalidad de la cohorte; contrariamente, medicación IECA (HR: 0,78; IC el 95%: 0,61-1,00), ARA-II (HR: 0,70; IC el 95%: 0,51-0,96) y estatinas (HR: 0,75; IC el 95%: 0,58-0,96) se asociaron con menor riesgo. Entre personas no institucionalizadas, cáncer, nefropatía y cardiopatía se asociaron con mayor riesgo y vacunación antigripal con menor riesgo.

Conclusión: En un área con relativamente baja incidencia de COVID-19, edad, institucionalización y múltiples comorbilidades aumentaron el riesgo/susceptibilidad de sufrir la COVID-19. Contrariamente, estatinas, inhibidores del sistema renina-angiotensina y vacunación antigripal se asociaron con menor riesgo.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), discovered in December 2019 following an outbreak of pneumonias in Wuhan, China, causes an infectious illness known as coronavirus disease 2019 (COVID-19). The World Health Organisation (WHO), due to the alarming levels of spread of the disease and its severity, declared it to be a pandemic on March 11, 2020.[1] Currently the disease continues to spread in the world, with almost 100 million confirmed cases in later January 2021.[2] In Spain there was a first wave in March–April that was considered contained on May 11, with a total of just over 250,000 diagnosed cases; the contagion curve grew again in June until reaching the maximum peak of second wave in mid-October and as of later January 2021, in the middle of the third wave, the Spanish Ministry of Health reports 2,705,001 cases and almost 58,000 deaths.[3]

There is much information updating COVID-19 surveillance epidemiological data (number of cases and deaths by demographic characteristics, accumulated incidences, ratios for positive laboratory testing, etc) but there is few population-based data on specific incidence and susceptibility for SARS-COV-2 infection in different population subgroups with distinct underlying—believed as at-risk—conditions.[2,3]

Earlier studies regarding clinical characteristics and prevalence of comorbidities among COVID-19 patients reported that cardiovascular disease (including hypertension), chronic respiratory disease, renal disease, cancer, diabetes mellitus, obesity and smoking were major risk factors for severe COVID-19. However, most of these results (mainly based on hospitalised severe cases) are likely confounded by age and other unadjusted variables (including other sociodemographic, medical or health care-related factors).[4–7]

Of note, COVID-19 patients managed as outpatients were generally poorly represented in COVID-19 research studies.[4–7] In this sense, a UK report based on a primary care cohort found that positive SARS-CoV-2 testing was associated with similar risk factors (except smoking) as described for severe COVID-19 in hospital settings.[8] Nevertheless, there is uncertainty about the possibility that some of these conditions although they increase the risk of severe COVID-19, may not "per se" increase the risk of SARS-COV-2 infection.[9]

In this context, we designed a large population-based cohort study aimed to investigate the incidence, clinical characteristics, susceptibility and risk profile of suffering COVID-19 among middle-aged and older adults (who supported the greatest burden of COVID-19 at this time) in the region of Tarragona across pandemic period. First-time analyses reporting earlier data have been published.[10,11] The present report updates population-based incidence data and risk of suffering laboratory-confirmed COVID-19 among cohort members by distinct underlying medical conditions (previous comorbidities, vaccinations' history and common chronic medications' use), reporting final data observed at the end of the planned study period (from 1st March to 30th June 2020).

Methods

Design, setting and study population

The design, setting and study population have been extensively described elsewhere.[10,11] Briefly, this is a population-based cohort study (began in April 2020) that included 79,083 persons ≥50 years-old in Tarragona area, whose total population (all-age) is 210,672 inhabitants.[12] The cohort incorporates all persons ≥50 years old assigned to 12 Primary Care Centres (PCCs) managed by the Institut Català de la Salut (ICS) in the study area (*Tarragonés, Alt Camp and Conca de Barberà* counties). The reference Hospital and Laboratory for the 12 participating PCCs were *Hospital Universitari Joan XXIII* and its Microbiological Department in the city of Tarragona. According to census data, the study cohort represents approximately 75% of inhabitants aged 50 years or older in the study area.[12]

Cohort members were followed since March 1st 2020 (date before the onset of the epidemic in the region), until the appearance of any study event (COVID-19 diagnosis or death), or until the end of 4-month follow-up (June 30, 2020). The study was approved by the Ethics Committee of the Foundation University Institute for Primary Health Care Research (IDIAP Jordi Gol, Barcelona, file

20/065-PCV) and was conducted according to the Helsinki Declaration and Spanish legislation on biomedical studies, data protection and respect for human rights.[13] Considering public health surveillance emergency, informed consent for all cohort members was waived.

Data sources

An institutional clinical research database earlier used for other cohort studies in the area (CAPAMIS),[14] was updated and became the primary data source for this COVID-19 epidemiologic report; it includes administrative and clinical data (coded according to the International Classification of Diseases 10th Revision, ICD-10), extracted from the PCCs' clinical records electronic system, that operates since the 2000s. We collected sociodemographic characteristics, previous comorbidities, chronic medications and vaccinations' history for cohort members in order to establish their baseline conditions (at March 1, 2020).

When the COVID-19 epidemic period onset in the area, two electronic alerts, linked to COVID-19 laboratory tests results and ICD-10 codes for disease suspicion (B34.2 and B97.29), were added to the electronic clinical records system of PCCs. Subsequently, both data sources were associated in the anonymised research database used for this report. Vital status for all cohort members was considered according to administrative data periodically updated in the electronic PCCs' clinical records (Fig. 1 shows Study scheme).

Outcomes

The main outcome was laboratory-confirmed COVID-19 diagnosed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or serological testing. For laboratory diagnosis of COVID-19, guidelines of the Health Department of the Generalitat de Catalunya were implemented.[15] Of note, the availability of PCR testing was scarce during the first weeks of epidemic period, and they were prioritised for severe cases (requiring hospital admission) and nursing-home residences (where several outbreaks took place), while less PCR tests were made among possible cases with mild symptoms managed as outpatient. For descriptive results we report suspected/presumptive COVID-19 cases (persons coded as clinical suspicion alone without PCR tested) and, additionally, COVID-19-excluded cases (PCR performed with a negative result) among cohort members across study period.

Covariates

Besides socio-demographic (age, sex and type of residence as community-dwelling/nursing-home), main covariates for this study were vaccinations' history (influenza vaccine in prior autumn, pneumococcal [pneumococcal polysaccharide vaccine - PPV23- and pneumococcal conjugated vaccine -PCV13-] or tetanus vaccination at any time) and presence of pre-existing comorbidities. The following comorbidities/underlying conditions were considered according to ICD-10 codes data registered in the electronic PCCs clinical records on 01/03/2020: neurological disease (including dementia and stroke), cancer (solid organ or haematological neoplasia diagnosed in past 5 years), chronic renal failure, systemic autoimmune rheumatic diseases (including rheumatoid arthritis and lupus), chronic respiratory disease (including chronic bronchitis/emphysema and/or asthma), chronic heart disease (including congestive heart failure, coronary artery disease and other cardiopathies), atrial fibrillation, chronic liver disease (including chronic hepatitis and cirrhosis), arterial hypertension, diabetes mellitus, hypercholesterolemia, obesity, alcoholism and smoking.

In addition, baseline use of some common chronic medications, which could be hypothetically related with physiopathological

mechanism of SARS-COV-2 infection or virulence (e.g., antihypertensive, antiplatelet/anticoagulant and/or anti-inflammatory drugs), were also considered as exposure covariables possibly related with the occurrence of COVID-19 for the present study. Thus, active medication treatments in each cohort member on 01/03/2020, coded according to the Anatomical, Therapeutic, and Chemical classification system (ATC) of the World Health Organization,[16] were identified from the patient treatment plan registered in the PCC's clinical records system, and included the following therapeutic groups: antihypertensive (diuretics, beta-blockers, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin II receptor blockers [ARBs], calcium channel blockers), statins, anticoagulants (warfarin and new oral anticoagulant drugs), antiplatelet drugs, antidiabetic drugs (insulin, oral antidiabetic drugs), inhaled respiratory drugs, antineoplastic agents, systemic corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), chloroquine/hydroxychloroquine, antihistamines, proton-pump inhibitors and benzodiazepines.[16] Criteria used to define and collect pre-existing conditions and chronic medications use are extensively described in an appendix elsewhere.[1] A comorbidity/medication was considered absent if it was not recorded.

Statistical analyses

Descriptive statistics included frequencies, percentages, means and standard deviations (SD). Incidence rates (IRs) for laboratory-confirmed COVID-19 cases were calculated as person-weeks, considering in the denominator the sum of the persons-time contributed for each cohort member during the study period (17.4 weeks). Confidence intervals (CIs) for IRs were calculated assuming a Poisson distribution for uncommon events. In bivariate analyses, baseline characteristics according to final presence/absence of study outcome (COVID-19 diagnosis) were compared using Chi-squared or Fisher's test as appropriate.
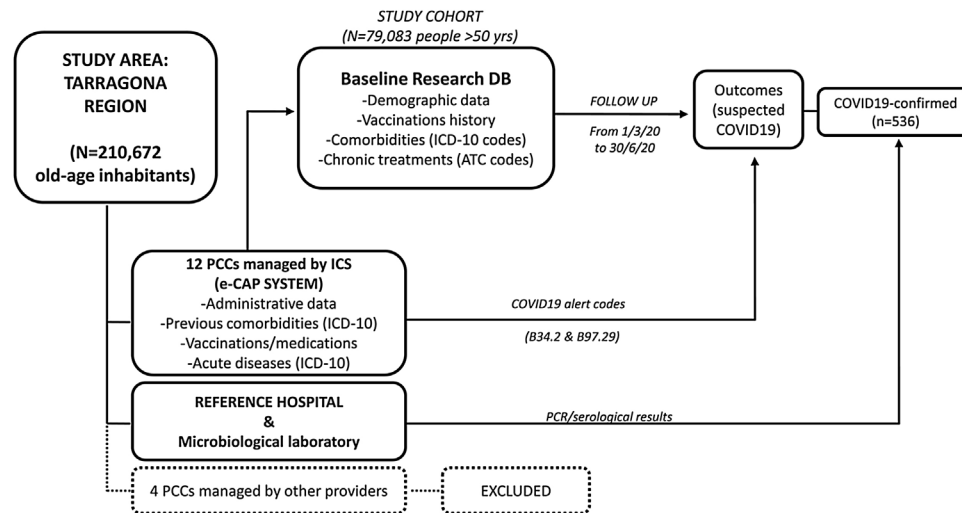
Cox regression analyses were used to calculate unadjusted, age & sex-adjusted and multivariable-adjusted hazard ratios (HRs) aimed at estimating the association between baseline exposure conditions and the time to the first outcome (laboratory-confirmed COVID-19) in cohort members throughout the study period (from 1st March to 30th June 2020). We included in exploratory multivariable Cox models all above mentioned exposure covariables (i.e., age, sex, residence, vaccinations' history, comorbidities/underlying conditions and medications use). The method to select a subset of variables to include in final models was the purposeful selection.[17] These models incorporate significant and confounder variables as well as all covariates judged clinically or epidemiologically relevant. We performed a main analysis with the total study cohort ($N = 79,083$) and two subgroup analyses restricted to community-dwelling people ($N = 77,669$) and nursing-home residents ($N = 1414$). Statistical significance was set at $p < 0.05$ (two-tailed). Analyses were performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA).

Results

Study cohort included 37,626 (47.6%) men and 41,457 (52.4%) women, with a mean age of 65.8 (SD: 11.3) years. Stratifying by age, 42,684 (54%) were 50–64 years and 10,386 (13.1%) were 80 years or more; by residence, 1414 (1.8%) were nursing-home residents and 77,669 (98.2%) community-dwelling individuals.

Total cohort members were followed for 1,356,358 persons-weeks (1,335,069 persons-weeks community-dwelling and 21,289 persons-weeks nursing-home residents).

Of the 79,083 cohort members, 4084 (5.2%) were PCR tested for SARS-COV-2 infection across the study period. Of them, 3577

E.M. Satué-Gracia, A. Vila-Córcoles, C. de Diego-Cabanes et al.

Medicina Clínica 158 (2022) 251–259

Fig. 1. Study scheme. PCC: primary care centres; ICS: Institut Castalà de la Salut; e-CAP: electronic primary care clinical records system; ICD. International classification of diseases, 10th revision; ATC: Anatomic & Therapeutic Classification for medications used.

(87.6%) had a negative result and 507 (12.4) a positive result (319 in community-dwelling and 188 in nursing-home residents). Additionally, 29 cohort members had a positive laboratory serological testing for SARS-COV-2 (twenty-six community-dwelling and three nursing-home residents). Two hundred and eighty-three cohort members had a suspected (clinically compatible) COVID-19 without laboratory testing.

Of the 536 laboratory-confirmed COVID-19 cases, 235 (43.8%) were men and 301 (56.2%) women, with a mean age of 74 years (SD: 14.4). By age groups, 177 (33.0%) occurred in those who were 50–64 years, 137 (25.6%) in those 65–79 years and 222 (41.4%) in aged 80 years or more. Three hundred and forty-five cases (64.4%) occurred in community-dwelling and 191 (35.6%) in nursing-home residents. The most prevalent comorbidities were hypertension (54.1%), cardiac disease (28.5%), obesity (25.2%), diabetes (23.5%), respiratory disease (14.9%) and neurological disease (14.7%).

Fig. 2 shows weekly distribution of COVID-19-confirmed cases and cumulative incidences at 7-day and 14-day across the 18 weeks of the study period.

Mean IR across study period was 39.5 (95% CI: 36.1–43.2) cases per 100,000 persons-week (24.1 in 50–64 years vs 30.6 in 65–79 years vs 127.0 in 80 years or older; 36.4 in men vs 42.3 in women; 25.8 in community-dwelling vs 897.2 in nursing-home residents).

By underlying conditions, maximum IRs (per 100,000 persons-week) emerged among those persons with neurological diseases (206.0) followed by atrial fibrillation (109.4), chronic renal failure (85.9), chronic heart disease (66.9), inflammatory bowel disease (66.0) and chronic respiratory disease (64.6). According to baseline chronic medications, maximum IRs appeared among those receiving diuretics (97.0), oral anticoagulants (87.3), insulin (83.1), and inhaled-respiratory therapy (72.1) (Table 1).

Table 2 shows unadjusted, age & sex-adjusted and multivariable adjusted analyses evaluating risk of suffering laboratory-confirmed COVID-19 in the whole study cohort. In the unadjusted analysis, many previous comorbidities and medications were associated with increased risk. However, after multivariable-adjustment, only age (HR: 1.01; 95% CI: 1.00–1.02), nursing-home residence (HR: 20.19; 95% CI: 15.98–25.51), neurological disease (HR: 1.35; 95% CI: 1.03–1.77), taking diuretics (HR: 1.39; 95% CI: 1.10–1.75), antiplatelet drugs (HR: 1.36; 95% CI: 1.05–1.76), benzodiazepines (HR: 1.24; 95% CI: 1.00–1.53) and history of PCV13 vaccination (HR: 1.74; 95% CI: 1.06–2.85) appeared significantly associated with increased risk. Smoking (HR: 0.57; 95%CI: 0.41–0.80), taking ACEIs (HR: 0.78; 95% CI: 0.61–1.00), ARBs (HR: 0.70; 95%CI: 0.51–0.96)

and statins (HR: 0.75; 95% CI: 0.58–0.96) appeared associated with a reduced risk.

Supplementary Tables S1 (incidence rate) and S2 (unadjusted and adjusted risks) show subgroup analyses restricted to community-dwelling individuals (N = 77,669). In the multivariable analysis focused on these individuals, chronic renal disease (HR: 1.50; 95% CI: 1.02–2.21), cancer (HR: 1.45; 95% CI: 1.05–2.01), cardiac disease (HR: 1.32; 95% CI: 0.98–1.79), taking diuretics (HR: 1.54; 95% CI: 1.11–2.13) and benzodiazepines (HR: 1.28; 95% CI: 0.97–1.68) were related to increased risk. Smoking (HR: 0.51; 95% CI: 0.35–0.74), receiving ACEIs (HR: 0.63; 95% CI: 0.45–0.89), statins (HR: 0.66; 95% CI: 0.49–0.90) and influenza vaccination in prior autumn (HR: 0.68; 95% CI: 0.51–0.92) were associated with decreased risk (Table S2).

Supplementary table* S3 shows subgroup analyses restricted to nursing-home residents (N = 1414). In the multivariable analysis, increasing age (HR: 1.03; 95% CI: 1.01–1.05), receiving oral antidiabetic drugs (HR: 1.79; 95% CI: 1.04–3.08), antineoplastic agents (HR: 2.51; 95% CI: 1.05–6.01) and influenza vaccination in prior autumn (HR: 1.56; 95% CI: 1.07–2.29) were associated with increasing risk. In contrast, taking ARBs (HR: 0.47; 95% CI: 0.25–0.87) and history of tetanus vaccination (HR: 0.63; 95% CI: 0.44–0.91) were associated with decreased risk.

Discussion

Population-based clinical data on susceptibility and risk of SARS-COV-2 infection is limited.[9,18] This large cohort study was aimed to assess population-based incidence of laboratory-confirmed COVID-19 among middle-aged and older adults with distinct underlying medical conditions in a well characterised geographic area (Tarragona region) during the first wave of the COVID-19 epidemic (March–June 2020), investigating possible relationships between pre-existing medical conditions with the susceptibility/risk of suffering COVID-19.

As main result, we found a mean IR of 39.5 laboratory-confirmed COVID-19 cases per 100,000 persons-week throughout study period, which is a relatively low incidence as compared to other Spanish or European regions during the same time period.[19,20]

During the study period (17.4 weeks since 1st March until 30th June 2020), approximately 5% of cohort members were PCR tested (with 12.4% positive results). Taking this data into account, and considering that PCR test were scarcely available in the study area for patients with less severe symptoms during the first weeks of
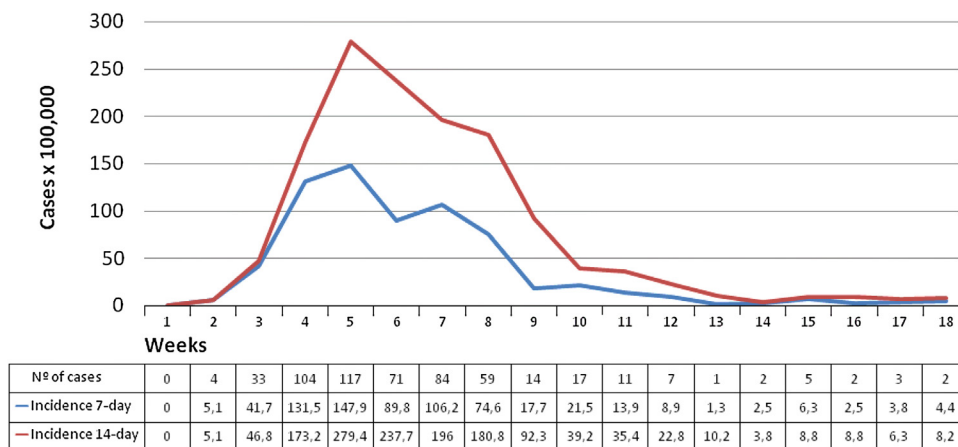
Nº of cases	0	4	33	104	117	71	84	59	14	17	11	7	1	2	5	2	3	2
—Incidence 7-day	0	5,1	41,7	131,5	147,9	89,8	106,2	74,6	17,7	21,5	13,9	8,9	1,3	2,5	6,3	2,5	3,8	4,4
—Incidence 14-day	0	5,1	46,8	173,2	279,4	237,7	196	180,8	92,3	39,2	35,4	22,8	10,2	3,8	8,8	8,8	6,3	8,2

Fig. 2. Weekly distribution of COVID-19-confirmed cases across study period (March 1st–June 30th 2020).

the epidemic period, the true incidence of COVID-19 was logically underestimated. Nevertheless, considering the relatively low number of presumptive cases (clinical suspicion alone without PCR performed), our data also suggests that the overall number of infected people could be considerably lower than initially speculated (as showed by the national seroprevalence study).[21]

Assuming this relatively little incidence, we found that increasing age, nursing-home residence, some pre-existing comorbidities (cancer, neurological, renal or cardiac disease and taking certain chronic medications (diuretics, antiplatelet drugs and benzodiazepines) were independent factors related to increased risk of suffering COVID-19. In contrast, cohort members receiving statins or ACEIs/ARBs (and, in the case of community-dwelling individuals, those vaccinated against influenza in prior autumn) presented, after multivariable-adjustment, a decreased risk.

Of note, in the crude analyses several covariates (comorbidities, medications and vaccinations) appeared significantly associated with increased risk/susceptibility of suffering COVID-19. However, for most of them the significance disappeared after age&sex-adjustment and only a few remained independently associated with an increased risk after multivariable adjustments. This highlights the importance of reporting adjusted data and note that differences in adjustment methods may explain, in part, the heterogeneous results reported to date evaluating the possible association between some pre-existing conditions and risk of COVID-19.[22]

At present, there is not clear evidence about possible clinical predisposing and protecting factors front SARS-COV-2 infection, and uncertainty surrounds this issue.[23]

If we consider demographic characteristics, apart from nursing-home residence that increased twenty-times the adjusted-risk of suffering laboratory-confirmed COVID-19, we found that age increased approximately 1–2% for each year the adjusted-risk of suffering COVID-19. While COVID-19 was more frequent in women, sex did not alter the risk of infection in multivariable analysis.

Considering pre-existing comorbidities, only neurological disease (basically patients with a history of dementia and/or stroke living in nursing-home residences) was associated with increased multivariable-adjusted risk of infection in the analysis of full cohort. Concomitantly, previous cancer, renal disease and cardiac disease emerged associated with increased risk in subgroup analysis restricted to community-dwelling individuals.

In the present study, chronic respiratory disease, diabetes, hypertension and obesity did not emerge independently associated with significant increased risk of suffering laboratory-confirmed COVID-19 after multivariable-adjusted analyses. There is general

accordance considering these conditions as major risk factors for poor prognosis in hospitalised COVID-19 patients, but there is few data assessing their role in predisposing for SARS-COV-2 infection.[24] Surprisingly, smokers presented the lowest specific incidence rate of COVID-19 in the present report, and smoking was associated with a reduced risk of COVID-19, both in multivariable analyses evaluating the total study cohort and in the restricted to community-dwelling individuals. This unexpected result could be due to possible selection bias (e.g., those who are current smokers may be healthier whereas those who suffered tobacco consequences may be currently non-smokers). Notably, active smoking has been linked with decreased odds of a positive result SARS-COV-2 test in other studies.[8] Opposite findings about poor prognosis among smokers with COVID-19 have been reported.[25,26]

Considering chronic medication use, receiving diuretics, antiplatelet drugs and benzodiazepines appeared associated with increased risk of suffering COVID-19. In contrast, taking statins and ACEIs or ARBs emerged associated with decreased risk. At onset of COVID-19 pandemic, after discovering that the host receptor for SARS-CoV-2 cell entry was the angiotensin-converting enzyme 2 (ACE2), it was feared that receiving ACEIs/ARBs could facilitate SARS-COV-2 infection and predispose to suffer severe COVID-19. However, most recent studies have concluded that there is no clinical or experimental evidence supporting that ACEIs or ARBs augment the susceptibility to/severity of COVID-19 at present.[7] Indeed, ACEIs/ARBs have been associated with lower incidence and/or improved outcomes in patients with lower respiratory tract infections, and with lower risk of all-cause mortality in COVID-19 hospitalised patients.[27]

Considering statins, while first studies reported opposite results, our data showing a decreased risk of laboratory-confirmed COVID-19 among people taking statins is in accordance with conclusions of a recent meta-analysis on this concern.[28] Anyway, caution is recommended until further evidence emerges surrounding statin use in COVID-19 patients.

Regarding other chronic medications that appeared associated with increased risk in the current study (i.e., diuretics, antiplatelet drugs and benzodiazepines), we have not a clear interpretation for this data. It is possibly due to an unresolved residual confounding, linked to unmeasured health-care-related factors or insufficient age-adjustment, but we also note that some of them (e.g., benzodiazepines) have already been reported associated with greater risk of pneumonia (common clinical manifestation in COVID-19 patients).

Antihistamines' use was not associated with any statistically significant change in the risk of suffering COVID-19 in the present

Table 1
Incidence of laboratory-confirmed COVID-19 cases according to baseline demographical and clinical characteristics in the total study cohort (N = 79,083). Tarragona region (Southern Catalonia, Spain), from 01/03/2020 to 30/06/2020.

Characteristic	Study population (N = 79,083) n (%)	Laboratory-confirmed COVID-19 cases (n = 536)		
		Univariate analysis n (%) p-value	Time follow-up (persons-week)	Incidence rate (95% CI)
Socio-demographic				
Age				
50–64 years	42,684 (54.0)	177 (33.0) <0.001	734,123	24.1 (20.8–28.0)
65–79 years	26,013 (32.9)	137 (25.6)	447,474	30.6 (25.8–36.2)
≥80 years	10,386 (13.1)	222 (41.4)	174,761	127.0 (110.2–146.2)
Sex				
Men	37,626 (47.6)	235 (43.8) 0.082	645,470	36.4 (32.1–41.3)
Women	41,457 (52.4)	301 (56.2)	710,888	42.3 (37.7–47.4)
Community-dwelling	77,669 (98.2)	345 (64.4) <0.001	1,335,069	25.8 (23.2–28.7)
Nursing-home residence	1414 (1.8)	191 (35.6)	21,289	897.2 (778.8–1032.7)
Comorbidities				
Neurological disease	2317 (2.9)	79 (14.7) <0.001	38,344	206.0 (164.4–257.5)
Renal disease	4476 (5.7)	65 (12.1) <0.001	75,629	85.9 (67.4–109.1)
Cancer	6630 (8.4)	67 (12.5) 0.001	112,481	59.6 (46.8–75.7)
Rheumatic disease	872 (1.1)	7 (1.3) 0.651	14,897	47.0 (18.8–96.8)
Inflammatory bowel disease	532 (0.7)	6 (1.1) 0.204	9097	66.0 (24.2–143.9)
Respiratory disease	7272 (9.2)	80 (14.9) <0.001	123,794	64.6 (51.6–80.8)
Cardiac disease	13,435 (17.0)	153 (28.5) <0.001	228,716	66.9 (57.1–78.3)
Atrial fibrillation	3786 (4.8)	70 (13.1) <0.001	63,962	109.4 (85.9–138.9)
Liver disease	1465 (1.9)	11 (2.1) 0.731	24,998	44.0 (22.0–78.8)
Diabetes	13,317 (16.8)	126 (23.5) <0.001	227,640	55.4 (46.1–66.5)
Hypertension	34,945 (44.2)	290 (54.1) <0.001	597,890	48.5 (43.3–54.4)
Hypercholesterolemia	27,314 (34.5)	181 (33.8) 0.707	468,535	38.6 (33.3–44.8)
Obesity	21,678 (27.4)	135 (25.2) 0.247	372,086	36.3 (30.6–43.0)
Smoking	12,750 (16.1)	41 (7.6) <0.001	219,518	18.7 (13.4–25.4)
Alcoholism	1796 (2.3)	11 (2.1) 0.733	30,774	35.7 (17.8–63.9)
Chronic medication use				
Diuretics	8481 (10.7)	139 (25.9) <0.001	143,357	97.0 (81.9–114.8)
Beta blockers	9571 (12.1)	87 (16.2) 0.003	163,450	53.2 (43.0–66.0)
ACEIs	16,419 (20.8)	114 (21.3) 0.772	281,514	40.5 (33.7–48.6)
ARBs	8869 (11.2)	54 (10.1) 0.401	152,376	35.4 (26.3–46.7)
Calcium channel blockers	6490 (8.2)	64 (11.9) 0.002	111,107	57.6 (44.4–74.9)
Statins	16,134 (20.4)	91 (17.0) 0.048	277,237	32.8 (26.5–40.7)
Oral anticoagulants	3912 (4.9)	58 (10.8) <0.001	66,424	87.3 (67.2–113.5)
Antiplatelet drugs	9154 (11.6)	108 (20.1) <0.001	155,957	69.2 (56.6–84.4)
Insulin	3042 (3.8)	43 (8.0) <0.001	51,741	83.1 (60.6–111.4)
Oral antidiabetic drugs	10,585 (13.4)	85 (15.9) 0.091	181,452	46.8 (37.9–58.0)
Inhaled respiratory drugs	6293 (8.0)	77 (14.4) <0.001	106,857	72.1 (57.5–90.1)
Antineoplastic agents	1614 (2.0)	12 (2.2) 0.745	27,691	43.3 (22.4–75.8)
Systemic corticosteroids	1252 (1.6)	10 (1.9) 0.599	21,030	47.6 (22.8–87.6)
NSAIDs	4321 (5.5)	21 (3.9) 0.114	74,152	28.3 (17.5–43.3)
Chloroquine	168 (0.2)	1 (0.2) 0.896	2867	34.9 (0.9–194.4)
Antihistamines	3264 (4.1)	15 (2.8) 0.121	56,243	26.7 (15.0–44.1)
Proton-Pump Inhibitors	17,931 (22.7)	183 (34.1) <0.001	305,566	59.9 (51.6–69.5)
Benzodiazepines	13,046 (16.5)	126 (23.5) <0.001	222,537	56.6 (47.1–67.9)
Vaccination's history				
Flu vaccine in prior autumn	22,606 (28.6)	258 (48.1) <0.001	385,668	66.9 (59.0–75.9)
PPV23	26,183 (33.1)	272 (50.7) <0.001	447,270	60.8 (53.6–68.9)
PCV13	1139 (1.4)	18 (3.4) <0.001	19,272	93.4 (55.4–147.6)
Tetanus	50,799 (64.2)	344 (64.2) 0.978	871,204	39.5 (35.5–43.9)

NOTE: p-Values in univariate analysis were calculated by chi-squared, or Fisher's test as appropriate, comparing percentages in the study population vs COVID-19 cases; IR denotes incidence rates per 100,000 persons-week; CIs denotes confidence intervals for incidence rates and were calculated assuming a Poisson distribution for uncommon events.

study. We note that antihistamines' use was associated (marginally significative) with a lower risk of COVID-19 in an earlier report,[11] but we also remark that it could be due to an alpha error considering that this final report has greater statistical power (since include more persons-time follow-up and greater number of events analysed).

Similar to data observed in earlier analyses, we found that influenza vaccination in prior autumn was associated with a reduction risk of suffering COVID-19 among community-dwelling individuals.[10] Conversely, it was associated with a greater risk in the subgroup of nursing-home residents (where a protective association appeared for those who had received tetanus vaccination). While these associations could be due to residual confounding related with unmeasured life-style or healthcare factors, further investigations are needed exploring a possible immunity-related mechanism explanation.[29,30]

Major strengths in this study were the large size and representativity of the study cohort, that included almost 80,000 people and represented about 75% of the entire population over 50 years in the area,[12] and the use of survival analysis methods to precisely asses

Table 2
Cox regression analyses assessing unadjusted, age & sex adjusted and multivariable-adjusted risks to suffer laboratory-confirmed COVID-19 in the total study cohort (N = 79,083). Tarragona region (Southern Catalonia, Spain) from 01/03/2020 to 30/06/2020.

Characteristic	Laboratory-confirmed COVID-19 cases (n = 536)		
	Unadjusted HR (95% CI)	Age & sex adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
Socio-demographic			
Age (continuous yrs)	1.06 (1.05–1.07)	1.06 (1.05–1.07)	1.01 (1.00–1.02)
Sex: women	1.16 (0.98–1.38)	1.00 (0.84–1.19)	0.89 (0.74–1.07)
Nursing-home residence	33.18 (27.80–39.59)	23.80 (19.18–29.53)	20.19 (15.98–25.51)
Comorbidities			
Neurological disease	5.86 (4.62–7.44)	3.01 (2.33–3.88)	1.35 (1.03–1.77)
Renal disease	2.33 (1.80–3.02)	1.09 (0.83–1.44)	1.01 (0.76–1.34)
Cancer	1.57 (1.22–2.03)	1.16 (0.90–1.50)	1.18 (0.91–1.55)
Rheumatic disease	1.19 (0.57–2.51)	1.07 (0.51–2.25)	1.29 (0.59–2.84)
Respiratory disease	1.74 (1.38–2.21)	1.36 (1.07–1.73)	1.16 (0.83–1.62)
Cardiac disease	1.97 (1.63–2.37)	1.21 (1.00–1.48)	0.99 (0.79–1.25)
Atrial fibrillation	3.02 (2.35–3.89)	1.57 (1.20–2.04)	1.25 (0.83–1.88)
Liver disease	1.12 (0.61–2.03)	1.26 (0.69–2.28)	1.13 (0.62–2.06)
Diabetes	1.52 (1.25–1.86)	1.13 (0.92–1.38)	1.09 (0.76–1.55)
Hypertension	1.49 (1.26–1.77)	0.83 (0.69–1.00)	0.97 (0.77–1.23)
Obesity	0.89 (0.73–1.08)	0.81 (0.66–0.98)	0.90 (0.73–1.11)
Smoking	0.43 (0.31–0.59)	0.69 (0.49–0.95)	0.57 (0.41–0.80)
Alcoholism	0.90 (0.50–1.64)	1.16 (0.64–2.13)	0.96 (0.52–1.77)
Chronic medications use			
Diuretics	2.95 (2.43–3.58)	1.71 (1.39–2.10)	1.39 (1.10–1.75)
Beta blockers	1.41 (1.12–1.78)	1.01 (0.80–1.28)	0.94 (0.73–1.22)
ACEIs	1.03 (0.84–1.27)	0.75 (0.61–0.92)	0.78 (0.61–1.00)
ARBs	0.89 (0.67–1.17)	0.62 (0.47–0.82)	0.70 (0.51–0.96)
Calcium channel blockers	1.52 (1.17–1.97)	1.04 (0.80–1.35)	1.19 (0.90–1.58)
Statins	0.80 (0.64–1.00)	0.60 (0.48–0.75)	0.75 (0.58–0.96)
Oral anticoagulants	2.35 (1.79–3.09)	1.29 (0.98–1.71)	1.18 (0.76–1.84)
Antiplatelet drugs	1.94 (1.57–2.39)	1.21 (0.97–1.51)	1.36 (1.05–1.76)
Insulin	2.20 (1.61–3.00)	1.64 (1.20–2.25)	1.24 (0.85–1.81)
Oral antidiabetic drugs	1.22 (0.97–1.54)	0.94 (0.74–1.18)	1.02 (0.70–1.48)
Inhaled respiratory drugs	1.96 (1.54–2.49)	1.43 (1.12–1.83)	1.23 (0.87–1.72)
Antineoplastic agents	1.10 (0.62–1.95)	1.04 (0.59–1.84)	0.94 (0.51–1.73)
Systemic corticosteroids	1.20 (0.64–2.24)	0.88 (0.47–1.65)	0.80 (0.42–1.53)
NSADs	0.71 (0.46–1.09)	0.84 (0.54–1.30)	1.13 (0.72–1.76)
Antihistamines	0.67 (0.40–1.12)	0.68 (0.41–1.14)	0.73 (0.43–1.22)
Proton-Pump Inhibitors	1.78 (1.49–2.13)	1.11 (0.92–1.34)	0.92 (0.74–1.15)
Benzodiazepines	1.56 (1.28–1.91)	1.19 (0.97–1.46)	1.24 (1.00–1.53)
Vaccination's history			
Flu vaccine in prior autumn	2.33 (1.97–2.76)	1.27 (1.05–1.54)	1.00 (0.80–1.25)
PPV23	2.09 (1.77–2.48)	0.85 (0.69–1.04)	1.05 (0.82–1.35)
PCV13	2.40 (1.50–3.84)	1.79 (1.12–2.87)	1.74 (1.06–2.85)
Tetanus	1.00 (0.84–1.19)	0.73 (0.61–0.87)	0.84 (0.68–1.03)

NOTE: HRs denotes Hazard ratios, and were calculated for those who had the condition as compared with those who had not the condition. In multivariable-adjusted analysis the HRs were adjusted for age (continuous years), sex, residence, comorbidities/underlying conditions and chronic medications use. CIs denote confidence intervals.

susceptibility and risk of suffering a SARS-COV-2 infection adjusting by important potential confounders (as socio-demographic, and medical underlying conditions clinically relevant).

Major limitations were related to its partially retrospective design and poor access to PCR tests at the beginning of the epidemic period in our setting, especially considering that the most specific diagnosis for COVID-19 is a positive PCR test. Moreover, its reliability depends on the correct collection of nasopharyngeal swabs, moment of collection, sensitivity of tests and guidelines for testing followed throughout the study period. Due to above mentioned scarce availability of PCR tests they were mainly performed in hospitalised/severe patients and in nursing homes (after some outbreaks were detected). Thereby, patients with mild symptoms (many of them without PCR done) have been logically underestimated in this study.

Despite the large size of the cohort, there were relatively few events (536 laboratory-confirmed COVID-19 cases), which limits statistical power. This is especially relevant in the subgroup of nursing-home residents where, even if great incidence occurred, only 191 confirmed COVID-19 cases were collected and this fact largely affects the precision of estimates (confidence intervals very wide). Notwithstanding all mentioned limitations, authors emphasise the added value that provide adjustments (age&sex and multivariable), not present in many other studies. Their importance is clearly evident if we compare, for example in Table 2, crude with adjusted results. Nevertheless, caution is needed before multivariable HRs interpretation. Obviously, the multivariable models may be incorrect and incomplete. Multivariable analyses have inherent limitations and a residual confounding in estimated coefficients (due to unobserved, unmeasured or unknown factors) may not be excluded.

We must consider that the study was conducted in a single geographic area; thus, specific incidence data cannot be directly extrapolated to other regions with distinct epidemic conditions. Nevertheless, we also note that the adjusted-risks estimated here may be helpful to better characterise the risk profile (socio-demographic, pre-existing conditions/comorbidities, chronic medication use) for suffering COVID-19 among middle-aged and older adults living in a setting with low/moderate intensity of COVID-19, as in the present study.

Conclusions

In summary, in this large population-based study that followed a cohort of 79,083 individuals ≥50 years old between March and June 2020 in Tarragona area, the incidence of laboratory-confirmed SARS-COV-2 infection was relatively low (39.5 cases per 100,000 persons-week) as compared with that of other Spanish regions during the first wave of COVID-19 pandemic. In this epidemic context (low incidence), our data supports that increasing age, nursing-home residence, pre-existing cancer, neurological, renal and cardiac disease are independent major predisposing conditions to suffer COVID-19 among middle-aged and older adults. Patients receiving diuretics, antiplatelet drugs and benzodiazepines were also at increased risk. Oppositely, patients taking statins, renin–angiotensin–aldosterone system inhibitors and those community-dwelling individuals that received influenza vaccination in prior autumn presented decreased risk.

Contributors

ESG and AVC wrote the manuscript; CDC, CTF, FGB, and IHG obtained data; ESG and AVR assessed outcomes and did statistical analyses; AVR edited the manuscript; OOG and FML revised the final version; AVC coordinated the study.

Funding

Conflict of interest

All authors, none declared.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.medcli.2021.03.027.

References

1. World Health Organisation (WHO). Listings of WHO's response to COVID-19. Available from: https://www.who.int/news/item/29-06-2020-covidtimeline [accessed 20.1.21].
2. World Health Organisation (WHO). Coronavirus Disease (COVID19). Weekly epidemiological update-27 January 2021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update–27-january-2021 [accessed 28.1.21].
3. Ministerio de Sanidad. Dirección General de Salud Pública. Centro de Coordinación de Alertas y Emergencias Sanitarias. Actualización n(300. Enfermedad por el coronavirus (COVID-19). 28.01.2021. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_300_COVID-19.pdf [accessed 28.1.21].
4. Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, Macho O, López GF, Robles MT, et al. COVID-19 Research Group of CSAPG Association between COVID-19 prognosis and disease presentation, comorbidities and chronic treatment of hospitalized patients. PLOS ONE. 2020;15:e0239571, http://dx.doi.org/10.1371/journal.pone.0239571.
5. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323:1574–81, http://dx.doi.org/10.1001/jama.2020.5394.
6. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–5, http://dx.doi.org/10.1016/j.ijid.2020.03.017.
7. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. PLOS ONE. 2020;15:e0238215, http://dx.doi.org/10.1371/journal.pone.0238215.
8. de Lusignan S, Dorward J, Correa A, Jones N, Akinyemi O, Amirthalingam G, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study. Lancet Infect Dis. 2020;20:1034–42, http://dx.doi.org/10.1016/S1473-3099(20)30371-6.
9. Lipsitch M, Swerdlow DL, Finelli L. Defining the epidemiology of Covid-19—studies needed. N Engl J Med. 2020;382:1194–6, http://dx.doi.org/10.1056/NEJMp2002125.
10. Vila-Córcoles Á, Ochoa-Gondar O, Torrente-Fraga C, Vila-Rovira Á, Satué-Gracia E, Hospital-Guardiola I, et al. Evaluación de la incidencia y perfil de riesgo de Covid-19 según comorbilidad previa en adultos ≥50 años del área de Tarragona. Rev Esp Salud Publica. 2020;94:e202006065.
11. Vila-Córcoles A, Ochoa-Gondar O, Satué-Gracia EM, Torrente-Fraga C, Gomez-Bertomeu F, Vila-Rovira A, et al. Influence of prior comorbidities and chronic medications use on the risk of COVID-19 in adults: a population-based cohort study in Tarragona, Spain. BMJ Open. 2020;10:e041577, http://dx.doi.org/10.1136/bmjopen-2020-041577.
12. Generalitat de Catalunya. Statistical institute of Catalonia. IDESCAT. Available at: https://www.idescat.cat/?lang=en [accessed 15.4.20].
13. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available from: https://www.wma.net/policies-post/wmadeclaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ [accessed 15.1.21].
14. Vila-Corcoles A, Hospital-Guardiola I, Ochoa-Gondar O, de Diego C, Salsench E, Raga X, et al. Rationale and design of the CAPAMIS study: effectiveness of pneumococcal vaccination against community-acquired pneumonia, acute myocardial infarction and stroke. BMC Public Health. 2010;10:25, http://dx.doi.org/10.1186/1471-2458-10-25.
15. Generalitat de Catalunya. Subdirecció General de Vigilància i Resposta a Emergències de Salut Pública. Procediment d'actuació enfront de casos d'infecció pel nou coronavirus SARSCoV-2. Available from: https://canalsalut.gencat.cat/web/.content/_A-Z/C/coronavirus-2019-ncov/material-divulgatiu/procediment-actuacio-coronavirus.pdf [accessed 16.4.20].
16. Who Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2020. Available from: https://www.whocc.no/atc_ddd_index/ [accessed 12.5.20].
17. Hosmer DW, Lemeshow S. Applied survival analysis. Regression modelling of time to event data. New York: John Wiley & Sons, 1999.
18. Koh WC, Naing L, Chaw L, Rosledzana MA, Alikhan MF, Jamaludin SA, et al. What do we know about SARS-CoV-2 transmission? A systematic review and meta-analysis of the secondary attack rate and associated risk factors. PLOS ONE. 2020;15:e0240205, http://dx.doi.org/10.1371/journal.pone.0240205.
19. Gobierno de España. Secretaría General de Sanidad. Dirección General de Salud Pública, Calidad e innovación. Centro de Coordinación de Alertas y Emergencias Sanitarias. Actualización n° 152. Enfermedad por el coronavirus (COVID-19). 30.06.2020. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_152_COVID-19.pdf [accessed 5.12.20].
20. European Centers for Disease Prevention and Control. Situation updates on COVID19. Available from: https://www.ecdc.europa.eu/en/covid-19/situation-updates [accessed 30.6.20].
21. Instituto de Salud Carlos III. Estudio ENE-COVID19: informe final. Estudio nacional de sero-epidemiología de la infección por SARS-CoV-2 en España. July 6, 2020. Available from: https://www.mscbs.gob.es/ciudadanos/ene-covid/docs/ESTUDIO_ENE-COVID19_INFORME_FINAL.pdf [accessed 30.7.20].
22. Yusuf E, Maiwald M. COVID-19, equipoise and observational studies: a reminder of forgotten issues. Infection. 2020:1–3, http://dx.doi.org/10.1007/s15010-020-01466-9.
23. Fakhroo AD, Al Thani AA, Yassine HM. Markers associated with COVID-19 susceptibility resistance, and severity. Viruses. 2020;13:45, http://dx.doi.org/10.3390/v13010045.
24. Centres for Disease Control and Prevention. Coronavirus Disease 2019 (COVID19). People with Certain Medical Conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html [accessed 23.2.21].
25. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, et al. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol. 2020;92:1915–21, http://dx.doi.org/10.1002/jmv.25889.
26. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). Eur J Intern Med. 2020;75:107–8, http://dx.doi.org/10.1016/j.ejim.2020.03.014.
27. Kreutz R, Algharably EAE, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Hypertension, the renin–angiotensin system, and the risk of lower respiratory

E.M. Satué-Gracia, A. Vila-Córcoles, C. de Diego-Cabanes et al.

Medicina Clínica 158 (2022) 251–259

tract infections and lung injury: implications for COVID-19. Cardiovasc Res. 2020;116:1688–99, http://dx.doi.org/10.1093/cvr/cvaa097.

28. Kow CS, Hasan SS. Meta-analysis of effect of statins in patients with COVID-19. Am J Cardiol. 2020;134:153–5, http://dx.doi.org/10.1016/j.amjcard.2020.08.004.

29. Salem ML, El-Hennawy D. The possible beneficial adjuvant effect of influenza vaccine to minimize the severity of COVID-19. Med Hypotheses. 2020;140:109752, http://dx.doi.org/10.1016/j.mehy.2020.109752.

30. Ietto G. SARS-CoV-2: reasons of epidemiology of severe ill disease cases and therapeutic approach using trivalent vaccine (tetanus, diphtheria and Bordetella pertussis). Med Hypotheses. 2020;141:109779, http://dx.doi.org/10.1016/j.mehy.2020.109779.