



# To clarify the safety profile of paracetamol for home-care patients with COVID-19: a real-world cohort study, with nested case–control analysis, in primary care

Francesco Lapi<sup>1</sup> · Ettore Marconi<sup>1</sup> · Ignazio Grattagliano<sup>2</sup> · Alessandro Rossi<sup>2</sup> · Diego Fornasari<sup>3</sup> · Alberto Magni<sup>2</sup> · Pierangelo Lora Aprile<sup>2</sup> · Claudio Cricelli<sup>2</sup>

Received: 3 June 2022 / Accepted: 11 July 2022 / Published online: 30 July 2022  
© The Author(s), under exclusive licence to Società Italiana di Medicina Interna (SIMI) 2022

## Abstract

**Background and objective** This study aimed to compare the prescribing patterns of paracetamol in COVID-19 with those for similar respiratory conditions and investigated the association between paracetamol use and COVID-19-related hospitalization/death.

**Methods** Using a primary care data source, we conducted a cohort study to calculate the incidence rate of paracetamol use in COVID-19 and for similar respiratory conditions in 2020 and 2019 (i.e. pre-pandemic phase), respectively. In the study cohort, we nested a case–control analyses to investigate the association between paracetamol use and COVID-19-related hospitalizations/deaths.

**Results** Overall, 1554 (33.4 per 1000) and 2566 patients (78.3 per 1000) were newly prescribed with paracetamol to treat COVID-19 or other respiratory conditions, respectively. Those aged 35–44 showed the highest prevalence rate (44.7 or 99.0 per 1000), while the oldest category reported the lowest value (17.8 or 39.8 per 1000). There was no association for early (OR = 1.15; 95% CI: 0.92–1.43) or mid-term (OR = 1.29; 95% CI: 0.61–2.73) users of paracetamol vs. non-users. Instead, the late users of paracetamol showed a statistically significant increased risk of hospitalization/death (OR = 1.75; 95% CI: 1.4–2.2).

**Conclusions** Our findings provide reassuring evidence on the use and safety profile of paracetamol to treat early symptoms of COVID-19 as in other respiratory infections.

**Keywords** Paracetamol · Prescribing pattern · Safety profile · Home-care · COVID-19

## Background

The SARS-CoV-2 pandemic is still burdening the healthcare system of several Western countries. Patients with mild-to-moderate COVID-19, for whom home-care treatment is requested, generally present flu-like symptoms such as fever,

pharyngitis, cough, rhinitis, headache, and myalgia [1, 2]. Among the available medications, paracetamol is recommended by the World Health Organization (WHO) [3], the National Institute for Health and Care Excellence (NICE) [4] as well as other regulatory agencies [5, 6] and scientific societies [7] among the mainstays to manage coronavirus-related early symptoms.

Nevertheless, there was conflicting and misleading communication [8, 9] on the pharmacotherapy for the home care of COVID-19. Some clinicians and researchers raised concerns on the safety profile of paracetamol when used in SARS-CoV-2 infections [10, 11]. They underlined that the potential depletion of glutathione (GSH) induced by paracetamol may even favour the pulmonary endothelium damages by SARS-CoV-2 [10, 12]. The authors therefore recommended to avoid the use of paracetamol to treat the early symptoms of COVID-19, and warned on the dramatic

✉ Francesco Lapi  
lapi.francesco@simg.it

<sup>1</sup> Health Search, Italian College of General Practitioners and Primary Care, Via del Sansovino 179, 50142 Florence, Italy

<sup>2</sup> Italian College of General Practitioners and Primary Care, Florence, Italy

<sup>3</sup> Department Medical Biotechnology and Translational Medicine, Università Degli Studi Di Milano, Milan, Italy

increase of use of this drug during the pandemic [10, 13]. Consistently, Suter et al. [11] reported significant reduction of hospital admission rate when non-steroidal anti-inflammatory drugs (NSAIDs) were administered in the first 72 h [11, 13] from the infection, and indicated that nimesulide, aspirin or celecoxib as the recommended choice instead of paracetamol. However, these positions were based on pre-clinical findings [12] with no clinical proof. Second, the studies supporting a greater effectiveness for an early use of NSAIDs [11] were undersized and might suffer from methodological flaws [14]. Third, the relationship between paracetamol-induced GSH consumption and COVID-19 severity might be clinically observed because of protopathic bias [15–18].

In order to clarify the place in therapy of paracetamol for the home care of COVID-19, we investigated the prescribing patterns of paracetamol for COVID-19 in 2020 as well as for other “similar” respiratory conditions being diagnosed in pre-pandemic phase. Then, we investigated the putative risk of COVID-19-related hospitalization/death due to paracetamol use, as well as the effect of protopathic bias on the results.

## Methods

### Data source

We used the Health Search Database (HSD) implemented by the Italian College of General Practitioners and Primary Care. In HSD, patients’ demographic details are linked using an encrypted unique identifier with medical records (diagnoses, tests performed, tests results, hospital admissions, etc.), drug prescriptions (trade name, dosage form, Anatomical Therapeutic Chemical classification (ATC) code, ministerial code, active substances, date of filled prescription, number of days’ supply), risk factors, lifestyle variables (Body Mass Index (BMI)), smoking habits, alcohol use) and date of death. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The encoding of the ambulatory procedures is performed in accordance with the *Nomenclature Tariffario*, a list of all outpatient specialist medical services and related tariffs, instituted by the Ministerial Decree in 1996.

At the time of the study, 747 GPs homogeneously distributed across all areas of Italy and covering almost 1,200,000 patients were selected. To be considered for participation in epidemiological studies, GPs are required to meet up-to-standard quality criteria related to the levels of coding, prevalence of well-known diseases, mortality rates, and years of recording. [19] Furthermore, a specific index (ITOT) is

used to verify and check the data quality registration in HSD every semester [20]. HSD has been adopted for various clinical research topics [21–24].

### Study population and design

To investigate the prescribing patterns of paracetamol, we formed two cohorts with individuals aged  $\geq 15$  years diagnosed with COVID-19 or other respiratory conditions (ICD-9-CM: 460\* (excluding 460/30), 465.9, 485\*, 480\*–487\* (excluding 480.9/60)) between January 1st and December 31st, 2019 and between January 1st–December 31st, 2020, respectively. The date of diagnosis was operationally defined as the index date. As no specific ICD-9-CM codes for COVID-19 were available, two new subcategories were introduced in HSD in May 2020: namely, 460/30, coding for SARS-CoV-2 infection of the upper respiratory tract, and 480.9/60 for SARS-CoV-2-related pneumonia. To capture cases that occurred before the introduction of these specific codes, we included codes for respiratory diseases (see codes mentioned above), which were likely used in 2020 to register COVID-19 cases. In this respect, the pandemic curve being obtained with HSD (see Supplementary Fig. S1), which was consistent with that revealed by national public health authorities, showed a relevant underestimation of COVID-19 cases for the first quarter of 2020 when confirmed diagnoses were included only. As such, “confirmed” cases were those using specific codes of COVID-19, while “probable” cases were formed by “confirmed” diagnoses along with those codifying other respiratory conditions being registered in the first period (up to April 2020) of the pandemic phase. We successfully adopted this approach in prior studies. [21]

To investigate the safety profile of paracetamol in COVID-19 and the role of protopathic bias [17] to explain the association between paracetamol use and an increased risk of COVID-19-related hospitalization/death, we formed a cohort of COVID-19 patients who were followed up with until the occurrence of these events whichever came first: hospitalization/death (index date), end of data availability (30 June 2021). Those who cumulated less than 15 days of follow-up were excluded, so allowing a biological rationale for paracetamol putative effect. In this cohort, we nested a case–control analysis in which cases were matched up to 10 controls according to age (5 year categories), gender, calendar period (month of the cohort entry) and duration of follow-up. Controls were assigned with the same date of the respective cases. In comparison to a time-dependent survival analysis, a nested case–control analysis is computationally more efficient, while producing odds ratios (OR) that are unbiased estimators of incidence rate ratios, with little or no loss in precision. Thus, while a cohort study using a survival analysis uses the full risk set (i.e. all patients still at risk of the event at the time of the case’s event), the nested

case–control analysis uses a random sample of patients (i.e. controls) from that same risk set. [25]

## Outcome definition

The incidence rate and therapeutic schedules of paracetamol (ATC: N02BE01; N02BE51 excluding “codeine” and “ibuprofen” from the description of active substance) use were quantified among patients with probable SARS-CoV-2 and other respiratory infections being diagnosed in 2020 and 2019, respectively.

We identified every SARS-CoV-2-related hospitalization and/or death occurring during follow-up. As HSD provides no information on causes of hospitalization/death, we adopted an algorithm to define this outcome as in prior studies [21]. Hospitalizations were those in which the terms “SARS-CoV-2”, “COVID\*”, “coron\*” were reported and manually verified in the code description. Fatal cases were those occurring within 30 days of the diagnosis of SARS-CoV-2. For the case–control analysis, we identified every prescription of paracetamol being registered between entry (i.e. diagnosis of COVID-19) and index date. We classified the use of paracetamol into three mutually-exclusive categories, nominally early (within 3 of the entry date), mid-term (from 4 to 7 days of the entry date) and late (> 7 days from the entry date) use. These categories were chosen according to the proposed definition for early treatment of COVID-19-related symptoms [6, 10, 11], which were consistent with the presumptive association between paracetamol and COVID-19 progression. As potential confounders, we calculated the individual HS-CoVid [21] by identifying demographic, lifestyle and clinical features composing this vulnerability score in the overall period preceding the entry date, inclusive. This prediction score was developed and validated by us using HSD, according to TRIPOD statements [26]. Namely, the coefficients being estimated for each determinant were linearly combined to form HS-CoVid for each patient. The concurrent use of NSAIDs, antibiotics, heparin and steroids, was defined in the period preceding or on the index date [7]. The use of NSAIDs was captured in the same time windows adopted for paracetamol.

## Data analysis

Continuous variables were reported as mean (SD), while categorical values as proportions. The incidence rate of paracetamol use was calculated by dividing the number of patients being diagnosed with “probable” COVID-19 and prescribed with paracetamol during follow-up (numerator) for those diagnosed with “probable” COVID-19 (denominator). The analysis was stratified by age (5 year bands) and gender. Dosage of paracetamol use was quantified for each prescription using the available strengths (i.e., 500 or 1000 mg) and

therapy instructions reported by GPs. The *Prescribed Daily Dose (PDD)* and the overall strength (in mgs) contained in every prescription allow for the calculation of mean duration (in days). The same calculations were conducted for the other respiratory conditions being registered in 2019.

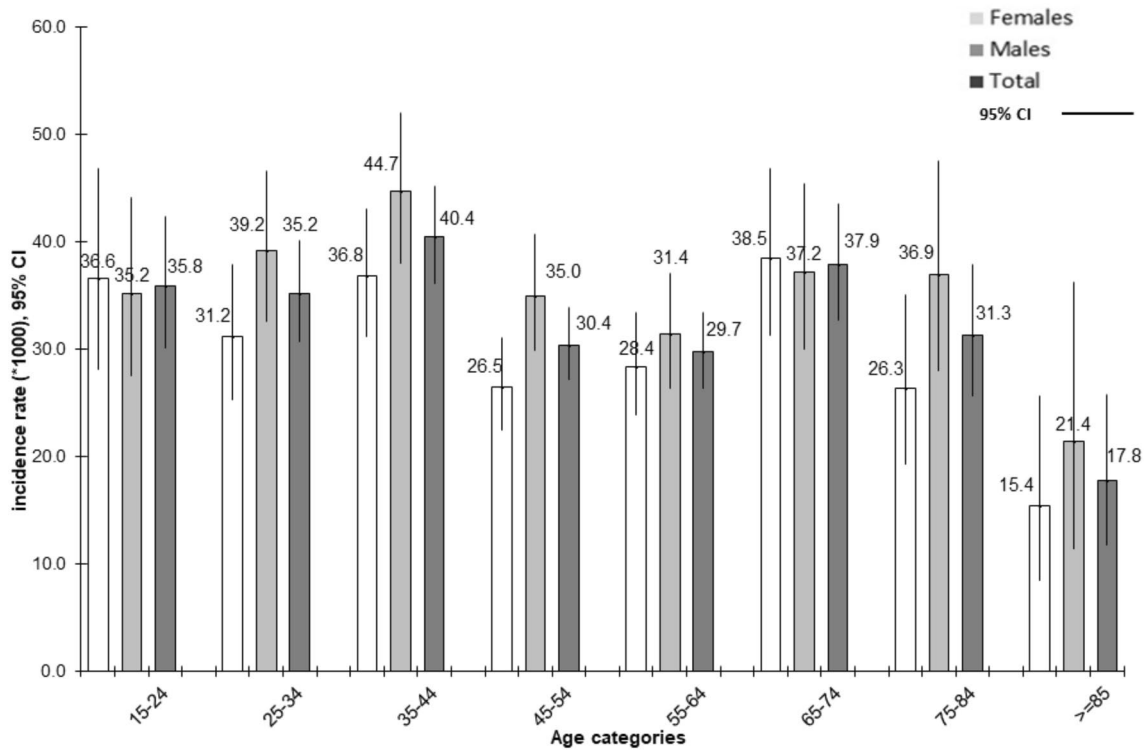
For the nested case–control analysis, a conditional logistic regression was adopted to estimate the ORs with related 95% confidence intervals (CI) to be exposed or unexposed to paracetamol among cases and related controls. The reference category was formed by non-users of paracetamol.

To verify the robustness of the results we conducted two sensitivity analyses. First, to consider the burden of misclassification for COVID-19 diagnoses, we re-ran the primary analyses by limiting cases to those classified as “confirmed”. Second, we carried out a probabilistic sensitivity analysis [27] to evaluate the effect on the results of exposure misclassification due to paracetamol use as OTC medication [28]. We assumed that younger individuals were featured by frequent use of OTC medications and less severe infection. We therefore hypothesized differential misclassification for paracetamol use by drawing the sensitivities and specificities from different uniform distributions for cases and controls [27]. For cases, we adopted distributions with an interval of equally probable values between 0.85 and 1 for both sensitivity and specificity. For controls, we adopted an interval of equally probable values ranging 0.55–1 (under-registration of OTC drug use in younger controls mainly) or 0.65–1 for sensitivity and specificity, respectively. We reported the median value (50th percentile) and 2.5th and 97.5th percentiles of the bias-adjusted OR.

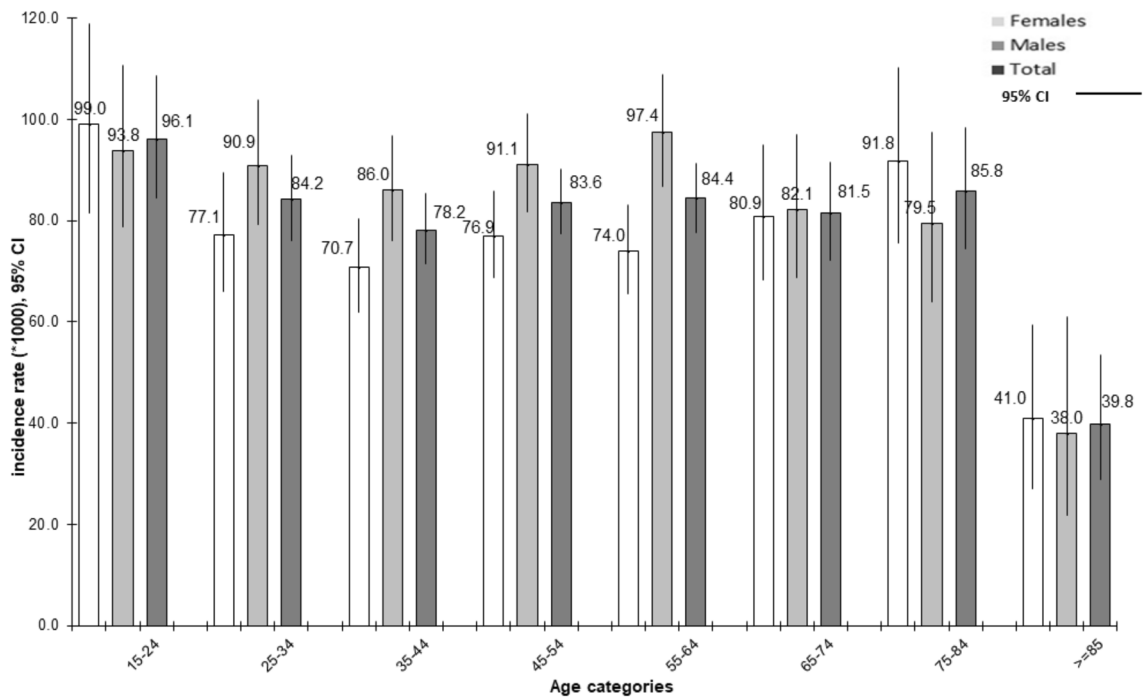
## Results

Overall, 46,522 probable cases of COVID-19 (mean age: 50.3 (SD: 17.7) years; 50.8% females) were identified in HSD in 2020. Among them, 1554 (33.4 per 1000) were newly prescribed with paracetamol to treat virus-related symptomatology. In 2019, we identified 32797 patients (mean age: 51.1 (SD: 19.1) years; 51.2% females) who suffered from other respiratory conditions. Among them, 2566 cases (78.3 per 1000) were prescribed with paracetamol.

Figure 1 depicts the incidence rates of paracetamol use among probable cases of COVID-19 being identified in HSD in 2020, taken as a whole and broken down by age and gender. Those aged 35–44 showed the highest prevalence rate (44.7 per 1000), while the oldest category reported the lowest value (17.8 per 1000). Males showed a higher use of paracetamol than females in almost all age categories except for those aged 15–24 and 65–74 years old. There was no age-related trend. Only those aged  $\geq 85$  years old reported lower incident use of paracetamol when compared with other age categories. This is indeed the only age category



**Fig. 1** Incidence rate of paracetamol use among ‘probable’ cases of COVID-19 according to age and gender



**Fig. 2** Incidence rate of paracetamol use by age and gender among cases of other respiratory infective conditions

showing a significant difference versus other categories given the absence of overlapped CIs with other subgroups.

Figure 2 depicts the incidence rates of paracetamol use for other respiratory infections in 2019. The incident

**Table 1** Paracetamol use and risk of COVID-19-related hospitalization/death

	Cases <i>N</i> =2756	Controls <i>N</i> =27,560	OR (95% CI) crude	OR (95% CI) adjusted*
Paracetamol non-use	2547 (92.42%)	26,031 (94.45%)	Ref	Ref
Paracetamol use after COVID-19 diagnosis (days)				
Early use:0–3	98 (3.56%)	890 (3.23%)	1.14 (0.92–1.41)	1.15 (0.92–1.43)
Mid-term use: 4–7	8 (0.29%)	59 (0.21%)	1.39 (0.66–2.91)	1.29 (0.61–2.73)
Late use:> 7	103 (3.74%)	580 (2.1%)	1.84 (1.48–2.29)	1.75 (1.40–2.18)

OR odds ratio, CI confidence interval

\*for HS-CoVid (vulnerability index), use of NSAIDs, heparin, steroids

users of paracetamol for these indications were higher than those observed for COVID-19, although the patterns of use appeared similar across all age categories. In specific, the highest rate of paracetamol use was observed among those aged 15–24 (99.0 per 1000) years, while the lowest incident use (39.8 per 1000) was seen among individuals aged  $\geq 85$  years. No age-related trend was observed for the other age categories. We calculated a mean number of prescriptions per patient equal to 1.03 (SD: 0.2) for ‘probable’ cases, respectively. Paracetamol strength of 500 or 1000 mg was prescribed in 8.9 and 46% of SARS-CoV-2 cases, respectively. For both dosages, the most frequent schedule was of 3 time daily (27.5 and 17.2% for 500 and 1000 mg, respectively). When the same analysis was run in 2019 using ICD9CM codes related to other respiratory conditions, the prevalence of use for paracetamol strength of 500 and 1000 mg was equal to 7.5 and 45.6%, respectively. The most frequent schedule was the three-time daily (27.5 and 17.2% for 500 and 1000 mg, respectively).

For the safety study, we identified a cohort of 78,117 cases of SARS-CoV-2 infections (mean age: 50.7 (SD: 17.8), 52.4% females) cumulating 22,918 person-months. Among them, we captured 2756 cases of COVID-19-related hospitalizations/deaths (incidence rate = 4 (95% CI: 3.9–4.2) per 1000 person-months). Table 1 depicts the association between paracetamol use, whose exposure categories were operationally defined at different times points following the date of COVID-19 diagnoses, and the risk of COVID-19-related hospitalization/death (see Supplementary Table S1 for case–control characteristics). There was no statistically significant association for early (OR = 1.15; 95% CI: 0.92–1.43) or mid-term (OR = 1.29; 95% CI: 0.61–2.73) users of paracetamol versus non- users. The late users of paracetamol showed a statistically significant increased risk of hospitalization/death (OR = 1.75; 95% CI: 1.40–2.18).

For what concerns the sensitivity analyses, the incidence rates of paracetamol use among ‘confirmed’ cases ( $n = 154$  out of 22655) of COVID-19 being identified in 2020 was higher in males than females for almost all age categories. The youngest subgroup showed the lowest incidence rate (4.0 per 1000), while those aged 65–74 reported the highest

rate of paracetamol use (11.2 per 1000) (Supplementary Fig. S2). For the nested case–control analysis, when COVID-19 cases were limited to confirmed diagnoses, the results were consistent with those obtained for the primary analysis (Supplementary Table S2). The probabilistic sensitivity analysis reported a median bias-adjusted OR for early use of paracetamol equal to 1.12 (2.5th and 97.5th percentile: 0.87 and 5.86) or 1.13 (2.5th and 97.5th percentile: 0.80 and 5.72) where systematic and systematic and random error were considered, respectively.

## Discussion

This is the first study investigating the place in therapy of paracetamol in the treatment of SARS-CoV-2-related symptoms. We found a lower incident use of paracetamol for COVID-19 when compared with other respiratory conditions in the pre-pandemic period. However, similar prescribing patterns were observed in pandemic and pre-pandemic phases. Younger and male patients were those majorly receiving paracetamol and the incident users decreased moving towards older-age categories. The early and mid-term use of paracetamol after COVID-19 diagnoses were not associated with an increased risk of COVID-19-related hospitalization and/or death, so providing further evidence that the significant association observed for late users was likely due to protopathic bias.

Recently, some works [13, 29] raised concerns on the safety profile of paracetamol when used to treat COVID-19-related symptoms. These statements were based on pre-clinical studies on paracetamol capacity to deplete GSH in pneumocytes and alveolar macrophages [12], thus limiting protection towards oxidative stress exerted by viral infections. Such a mechanism should explain the association between paracetamol use and the increased risk of severe pneumonia in COVID-19 patients [30]. Nevertheless, a residual amount of paracetamol (up to 15% at most) is usually undergone to the oxidative metabolism involving GSH, and the daily dosage able to cause a relevant depletion of

GSH should reach 15 g/daily (for an adult of 65–70 kgs), which is fivefold higher than the maximum allowed daily dose [31]. It is well known that paracetamol toxicity occurs with a dose-dependent mechanism and that cellular GSH depletion follows the excess production of the main toxic intermediate (NAPQI) when paracetamol doses exceed cellular GSH reserve. Such a mechanism has been proven as cause of acute liver injury, where NAPQI generation from paracetamol metabolism predominantly occurs [32]. In addition, there are no clinical studies supporting the association between paracetamol use and an increased risk of COVID-19-related complications.

The same authors [10, 29], supported the early use of some NSAIDs or COXIBs [30] in place of paracetamol. This position was based on an explorative study whose results have been largely discussed because of methodological concerns [14]. In this respect, Bonferroni-adjusted p-values were adopted for dependent (secondary) outcomes, so violating the main assumption of Bonferroni's correction [33]; the exposure categories were matched by propensity score but there had details on matching procedures and related performance [34]. In specific, the small sample size ( $n=90$ ) of the study cohort could have led to unbalanced confounders between treatment and control group, as observed for dyspnoea proportions (20 vs. 36.7% p value = 0.020). As such, the control group artificially showed a greater incidence rate of hospitalization because it featured more severe SARS-CoV-2 infections at the baseline than treatment group.

Then, as demonstrated by us for late users, the hypothetical relationship between paracetamol and COVID-19-related progression might have been clinically observed because of protopathic bias [17, 18]. A significant proportion of patients were prescribed with paracetamol because of increasing symptomatology in the time-window closely preceding the hospital admission. Thus, medications use to relieve fever and/or pain is erroneously associated with the occurrence of negative outcomes.

With the present study, we attempted to clarify the misleading messages stemming from the aforementioned publications, which are clearly inconsistent with what is recommended by WHO [3], and other public health authorities [4–6]. As a whole, GPs seem to prescribe paracetamol for COVID-19 as in other respiratory conditions, and we found no association with early use of paracetamol in COVID-19 and an increased risk hospitalization/death.

This study suffers from limitations as well. First, in the first quarter of 2020, GPs contributing to the HSD could not formally register COVID-19 patients as such. When we limited the analysis to confirmed cases of COVID-19, we still obtained consistent results. Second, this analysis was conducted using data of 2020 and 2021 (first semester). As such, they cannot be immediately applied to the Omicron variant. Nevertheless, there are no different patterns of early

symptoms between previous and current variants given the high vaccine coverage [35]. As such, there is no reason to imagine a different safety profile for paracetamol when used with the Omicron variant. Third, prescriptions of paracetamol for COVID-19 might be underestimated because it is not fully reimbursed. Nevertheless, the exposure misclassification due to paracetamol use as an OTC drug [28] might have caused biased results towards the null. When we conducted probabilistic sensitivity analysis [27], the bias-adjusted OR were consistent with those obtained for the primary analysis. Finally, the analysis was not fully adjusted for the anti-COVID vaccine effect, which was incepted among older adults in 2021. We found only eight cases exposed to paracetamol in 2021, demonstrating a negligible effect likely due to vaccine exposure.

In conclusion, our findings provide reassuring evidence on the safety profile of paracetamol to treat early symptoms of COVID-19 as in other respiratory infections. This result is particularly relevant given the characteristics of last Omicron variant, whose infectious spread is currently responsible for a quick and sensible increased number of COVID-19 patients needing home care.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s11739-022-03054-1>.

**Authors contribution** FL, IG, AR, DF, EM, AM, PLA and CC: have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. FL, EM, IG, DF, PLR and CC: have been involved in drafting the manuscript or revising it critically for important intellectual content. CC: is responsible for the integrity of the work, and he given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. FL: agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Funding** This article was supported by the Italian College of General Practitioners and Primary Care.

**Availability of data and materials** Not applicable.

## Declarations

**Conflict of interest** FL and EM provided consultancies in protocol preparation for epidemiological studies and data analyses for Angelini, Pfizer, and GSK. AR, IG, AM, PLA, and CC provided clinical consultancies for Angelini, Pfizer, and GSK. DF has no conflict of interest to disclose.

**Ethical approval** According to a by-law on the classification and implementation of observational drug-related research, as issued by the Italian National Drug Agency (an entity belonging to the Italian Ministry of Health), the present study does not require approval by an Ethics Committee in Italy (Italian Drug Agency note of 3 August 2007). This study followed the principles of the Declaration of Helsinki and com-

pliant with the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) Guide on Methodological Standards in Pharmacoepidemiology.

**Consent to participate** The database is fully anonymized.

**Consent for publication** Not applicable.

## References

- Elliott J, Whitaker M, Bodinier B et al (2021) Predictive symptoms for COVID-19 in the community: REACT-1 study of over 1 million people. *PLOS Med* 18:e1003777. <https://doi.org/10.1371/JOURNAL.PMED.1003777>
- Dinnes J, Deeks JJ, Berhane S et al (2021) Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. *Cochrane Database Syst Rev*. <https://doi.org/10.1002/14651858.CD013705.PUB2>
- Home care for patients with suspected or confirmed COVID-19 and management of their contacts. [https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-\(ncov\)-infection-presenting-with-mild-symptoms-and-management-of-contacts](https://www.who.int/publications/i/item/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts). Accessed 21 Feb 2022
- NICE Overview | COVID-19 rapid guideline: managing COVID-19 | Guidance | NICE. <https://www.nice.org.uk/guidance/ng191>. Accessed 20 Feb 2022
- CDC Treatments Your Healthcare Provider Might Recommend if You Are Sick | CDC. <https://www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html>. Accessed 20 Feb 2022
- AIFA Medicines usable for treatment of COVID-19 disease | Italian Medicines Agency. <https://www.aifa.gov.it/en/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della-malattia-covid19>. Accessed 22 Feb 2022
- DrI DG, A R et al (2021) How to treat COVID-19 patients at home in the Italian context: an expert opinion. *Infect Dis Rep*. <https://doi.org/10.3390/IDR13010028>
- Tuccori M, Convertino I, Ferraro S et al (2020) The impact of the COVID-19 “Infodemic” on drug-utilization behaviors: implications for pharmacovigilance. *Drug Saf* 43:699–709. <https://doi.org/10.1007/S40264-020-00965-W>
- Enners S, Gradl G, Kieble M et al (2021) Utilization of drugs with reports on potential efficacy or harm on COVID-19 before, during, and after the first pandemic wave. *Pharmacoepidemiol Drug Saf* 30:1493–1503. <https://doi.org/10.1002/pds.5324>
- Pandolfi S, Simonetti V, Ricevuti G, Chirumbolo S (2021) Paracetamol in the home treatment of early COVID-19 symptoms: a possible foe rather than a friend for elderly patients? *J Med Virol* 93:5704–5706
- Suter F, Consolaro E, Pedroni S et al (2021) A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: a retrospective observational matched-cohort study. *EClinicalMedicine* 37:100941
- Dimova S, Hoet PHM, Dinsdale D, Nemery B (2005) Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human alveolar macrophages and type II pneumocytes in vitro. *Int J Biochem Cell Biol* 37:1727–1737. <https://doi.org/10.1016/J.BIOCEL.2005.03.005>
- Pandolfi S, Chirumbolo S, Ricevuti G et al (2022) Home pharmacological therapy in early COVID-19 to prevent hospitalization and reduce mortality: time for a suitable proposal. *Basic Clin Pharmacol Toxicol* 130:225–239. <https://doi.org/10.1111/bcpt.13690>
- Battaglia A Un algoritmo terapeutico domiciliare per prevenire i ricoveri? I risultati possono essere dovuti a sbilanciamento e a errore random - E&P Repository. <https://repo.epiprev.it/index.php/download/un-algoritmo-terapeutico-domiciliare-per-prevenire-i-ricoveri-i-risultati-possono-essere-dovuti-a-sbilanciamento-e-a-errore-random/>. Accessed 21 Feb 2022
- Prada L, Santos DC, Baião RA et al (2021) Risk of SARS-CoV-2 Infection and COVID-19 Severity Associated With Exposure to Nonsteroidal Anti-Inflammatory Drugs: Systematic Review and Meta-Analysis. *J. Clin. Pharmacol*
- Faillie JL (2015) Indication bias or protopathic bias? *Br J Clin Pharmacol* 80:779–780. <https://doi.org/10.1111/BCP.12705>
- Tamim H, Tahami Monfared AA, LeLorier J (2007) Application of lag-time into exposure definitions to control for protopathic bias. *Pharmacoepidemiol Drug Saf* 16:250–258. <https://doi.org/10.1002/PDS.1360>
- Vaja R, Chan JSK, Ferreira P et al (2021) The COVID-19 ibuprofen controversy: a systematic review of NSAIDs in adult acute lower respiratory tract infections. *Br J Clin Pharmacol* 87:776–784. <https://doi.org/10.1111/BCP.14514>
- Lawrenson R, Williams T, Farmer R (1999) Clinical information for research; the use of general practice databases. *J Public Health Med* 21:299–304
- Bianchini E, Brignoli O, Cricelli C VIII Report Health Search. Available at: [http://healthsearch.it/documenti/Archivio/Report/VIIIReport\\_2013-2014/index.html](http://healthsearch.it/documenti/Archivio/Report/VIIIReport_2013-2014/index.html).
- Lapi F, Domnich A, Marconi E et al (2021) Predicting the risk of severe COVID-19 outcomes in primary care: development and validation of a vulnerability index for equitable allocation of effective vaccines. *Expert Rev Vaccines*. <https://doi.org/10.1080/14760584.2022.2019582>
- Lapi F, Simonetti M, Michieli R et al (2012) Assessing 5-year incidence rates and determinants of osteoporotic fractures in primary care. *Bone*. <https://doi.org/10.1016/j.bone.2011.09.048>
- Guglielmi V, Bellia A, Pecchioli S et al (2016) What is the actual epidemiology of familial hypercholesterolemia in Italy? *Int J Cardiol*, Evidence from a National Primary Care Database. <https://doi.org/10.1016/j.ijcard.2016.08.269>
- Cricelli C, Mazzaglia G, Samani F et al (2003) Prevalence estimates for chronic diseases in Italy: exploring the differences between self-report and primary care databases. *J Pub Health Med* 25:254–257
- Breslow NE (1996) Statistics in epidemiology: the case-control study. *J Am Stat Assoc*. <https://doi.org/10.1080/01621459.1996.10476660>
- Collins GS, Reitsma JB, Altman DG, Moons KGM (2015) Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *J Clin Epidemiol* 68:134–143. <https://doi.org/10.1016/j.jclinepi.2014.11.010>
- Orsini N, Bellocco R, Bottai M et al (2008) A tool for deterministic and probabilistic sensitivity analysis of epidemiologic studies. *Stata J* 8:29–48
- Hempenius M, Groenwold RHH, de Boer A et al (2021) Drug exposure misclassification in pharmacoepidemiology: sources and relative impact. *Pharmacoepidemiol Drug Saf* 30:1703–1715. <https://doi.org/10.1002/pds.5346>
- Suter F, Consolaro E, Pedroni S et al (2021) A simple, home-therapy algorithm to prevent hospitalisation for COVID-19 patients: a retrospective observational matched-cohort study. *EClinicalMedicine*. <https://doi.org/10.1016/J.ECLINM.2021.100941>
- Pandolfi S, Chirumbolo S (2021) Home therapy of COVID-19 at the earliest may greatly prevent hospitalization. *Basic Clin Pharmacol Toxicol* 129:395–396. <https://doi.org/10.1111/bcpt.13650>

31. Mitchell JR, Jollows DJ (1975) Metabolic activation of drugs to toxic substances. *Gastroenterology* 68:392–410. [https://doi.org/10.1016/S0016-5085\(75\)80025-4](https://doi.org/10.1016/S0016-5085(75)80025-4)
32. Kennon-McGill S, McGill MR (2018) Extrahepatic toxicity of acetaminophen: critical evaluation of the evidence and proposed mechanisms. *J Clin Transl Res* 3:297–310
33. Ranstam J (2016) Multiple *P*-values and Bonferroni correction. *Osteoarthritis Cartil* 24:763–764. <https://doi.org/10.1016/j.joca.2016.01.008>
34. Schneeweiss S (2006) Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 15:291–303. <https://doi.org/10.1002/pds.1200>
35. Collie S, Champion J, Moultrie H et al (2022) Effectiveness of BNT162b2 vaccine against omicron variant in South Africa. *N*

Engl J Med 386:494–496. [https://doi.org/10.1056/NEJMC2119270/SUPPL\\_FILE/NEJMC2119270\\_DISCLOSURES.PDF](https://doi.org/10.1056/NEJMC2119270/SUPPL_FILE/NEJMC2119270_DISCLOSURES.PDF)

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.