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LETTER TO THE EDITOR

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The widest use of paracetamol in home therapy might have actually increased the occurrence of severe forms of COVID-19 in Italy, affecting hospitalization and death rates

To the Editor,

A recent contribution by Perico et al. recommended the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) in the early stage of severe acute respiratory syndrome coronavirus 2(SARS-CoV2) infection, preventing the onset of a severe form of COVID-19 and hence reducing the hospitalization rate and the risk of mortality.[1] Many previous reports from the same group[2,3] and from ours,[4] showed that the use of paracetamol, as recommended by the Italian Ministry of Health since November 30, 2020, usually associated with the advice to monitor one's own developing symptoms at home ("watchful waiting"), increased the risk to be hospitalized. This risk usually was due to symptoms worsening, for which the assumption of paracetamol has been indicated as a major con-causative factor.[3,5] Usually, people with a mild fever use paracetamol as the elective pharmaceutical to relief painful and discomfort related with COVID-19 early symptoms.

Anyway, on November 30, 2020, referring to publicly retrievable data from the Italian Government, when the first release of the Italian Ministry of Health on home therapy was published, the number of SARS-CoV2 positive quarantined people was 751 540, on a total 1 601 554 of SARS-CoV2 positive subjects and 33 187 individuals hospitalized with symptoms, whereas 3744 patients were in the intensive therapy units (ITUs) and 55 576 individuals listed in the COVID-19-caused deceases. On that time, the estimated relative risk (RR) to be hospitalized in ITUs, starting from the first mild symptoms at home and being quarantined, was RR = 0.3174 (CI_{95} = 0.3079−0.3272, z = 73.931, p < 0.0001).

On April 26, 2021, a second release of the Italian Ministry of Health on home therapy recommendations, added the word NSAIDs alongside the possibility to use paracetamol. Revisions followed the criticism against the use of paracetamol in the many outcries from numerous doctors' associations, who led to administrative court trials, summons in the Senate and contradictory verdicts. On that time 250 633 people were quarantined (on a total of 4 202 827 positive from the beginning of pandemic), 8118 hospitalized with severe symptoms, 1278 patients were in ITUs and 125 622 were deceases, since then. The RR to be hospitalized in ITUs starting from home where symptoms started, was RR = 2.4163 (CI_{95} = 2.2959−2.5430), z = 33.837, p < 0.0001).

Moreover, on November 30, 2021, quarantined SARS-CoV2 positive subjects were 188 360 (on a total of 5 028 547 screened positive individuals), 5227 hospitalized, 683 in ITUs and 133 828 deceases. On that day the estimated RR was RR = 3.2008 (IC_{95} = 2.9824−3.4352, z = 32.266, p < 0.0001).

The National Observatory for Medicines (OSMED) data for 2020 reported that each Region in Italy showed a marked increase in paracetamol Defined Daily Dose (DDD) compared to that of NSAIDs.[6] The mean % of paracetamol DDD ratio on each specific population of Italian Regions was 4.14 ± 0.94 SD, whereas for NSAIDs the value was 2.56 ± 0.76 SD. Medians were 3.57% and 2.31%, respectively.

When a correlation test (Pearson's test) was performed between the delta paracetamol/NSAIDs (calculated on the ratio % $DDD_{pharmaceutical}$/population) and the ratio% (COVID-19 hospitalized/SARS-CoV2 positive quarantined) people, the value of R was 0.5228 (p = 0.15031). The increase in the DDD of paracetamol respect to NSAIDs positively correlated with the increase in the number of subjects hospitalized due to COVID-19 symptoms respect to SARS-CoV2 positive quarantined people at home.

The mean value of this delta was 1.58 ± 0.81 SD and the mean value of the ratio % hospitalized/quarantined was 6.75 ± 7.76 SD. Outliers removal leads the Pearson's correlation test to R = 0.648 (p = 0.003636).

Table 1A summarizes the RRs to be hospitalized related with the use of paracetamol and NSAIDs, according to OSMED data. Data of RRs for each Italian Region/District usually involved in COVID-19 public reports from the Italian Minister of Health, are also reported (Table 1B).

Finally, considering that a strong positive correlation can be demonstrated between COVID-19 hospitalized patients and COVID-19 deaths, as R = 0.8655 (p < 0.0001) at the Pearson's correlation test, speculation might be forwarded about the possibility that the higher use of paracetamol was a con-causative factor also of COVID-19 deaths in Italy.

These preliminary data support, on the field, many previous evidence warning about the risk in using paracetamol to address the early symptoms of SARS-CoV2 infection at home.

TABLE 1A Correlation between the incorrect use of paracetamol and relative risk (RR) to be hospitalized

	November 30, 2020 (before the first Minister of Health's issue)	Quarantined people 751 540 Hospitalized with symptoms 33 187 Intensive Therapy Units (ITUs) 3744 Deceases 55 576 RR to be hospitalized in ITUs 0.3174	Paracetamol usage in the pandemic peaks (year 2020) = ≥ 36 packages/100.000/die NSAIDs usage in the pandemic peaks (year 2020) = ≥ 34 packages/100.000/die
	April 21, 2021 (following the first Minister of Health's issue)	Quarantined people 250 633 Hospitalized with symptoms 8118 Intensive Therapy Units (ITUs) 1278 Deceases 125 622 RR to be hospitalized in ITUs 2.4163 (on Apir 26, 2021) RR to be hospitalized in ITUs 3.2008 (on November 30, 2021)	Paracetamol usage in the pandemic peaks (year 2020) = ≥ 40 packages/100.000/die NSAIDs usage in the pandemic peaks (year 2020) = ≥ 31 packages/100.000/die

TABLE 1B Forecast relative risks (RR) values to be hospitalized referred to the maximal % of paracetamol consumed in each Italian Region[a]

Lombardia RR = 3.3115 (CI95 = 3.0998–3.5376) $p < 0.0001$	Veneto RR = 5.6330 (CI95 = 5.1726–6.1345) $p < 0.0001$
Piemonte RR = 2.8776 (Ci95 = 2.7243–3.606) $p < 0.0001$	Campania RR = 22.5890 (CI95 = 20.953-24.352) $p < 0.0001$
Emilia-Romagna RR = 4.8568 (Ci95 = 4.5148–5.2248) $p < 0.0001$	Lazio RR = 8.1459 (Ci95 = 7.6762–8.6445) $p < 0.0001$
Toscana RR = 1.7940 (Ci_{95} = 1.5327-2.1000) $p < 0.0001$	Sicilia RR = 11.4642 (Ci_{95} = 10.5144–12.4999) $p < 0.0001$
Puglia RR = 12.4268 (Ci_{95} = 11.5297–13.3937) $p < 0.0001$	Liguria RR = 1.9859 (Ci_{95} = 1.7401-2.2664) $p < 0.0001$
Friuli-Venezia Giulia RR = 3.4331 (Ci_{95} = 2.9182–4.0389) $p < 0.0001$	Marche RR = 5.8084 (Ci_{95} = 4.9317–6.409) $p < 0.0001$
Abruzzo RR = 6.6715 (Ci_{95} = 5.6535–7.8728) $p < 0.0001$	Sardegna RR = 8.5951 (Ci_{95} = 7.3400–10.0650) $p < 0.0001$
Bolzano RR = 8.1360 (Ci_{95} = 5.3407–12.3944) $p < 0.0001$	Umbria RR = 5.3962 (Ci_{95} = 4.5472–6.4038) $p < 0.0001$
Calabria RR = 12.9321 (Ci_{95} = 10.7642–15.5365) $p < 0.0001$	Trento RR = 0.1935 (Ci_{95} = 0.1188–0.3153) $p < 0.0001$
Basilicata RR = 22.7684 (Ci_{95} = 16.6599–31.1166) $p < 0.0001$	Valle d'Aosta RR = 1.5948 (Ci_{95} = 1.1128–2.2856) $p = 0.0110$
Molise RR = 11.5914 (Ci_{95} = 7.5097–17.8917) $p < 0.0001$	

[a]Exposed = [Symptomatic hospitalized × % paracetamol used]/total symptomatic hospitalized]
Non exposed = [Hospitalized/Quarantined].

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Raw and elaborated data used for described results are available at the links indicated in the refs list and by the Corresponding Author, who let them known any time on request.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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