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Covid-19 and the role of smoking: the protocol of the multicentric prospective study COSMO-IT (COvid19 and SMOking in ITaly)

Maria Sofia Cattaruzza[1], Giuseppe Gorini[2], Cristina Bosetti[3], Roberto Boffi[4], Alessandra Lugo[5], Chiara Veronese[4], Giulia Carreras[2], Claudia Santucci[5], Chiara Stival[5], Roberta Pacifici[6], Vincenzo Zagà[7], Silvano Gallus[5] and the COSMO-IT Investigators[8]*

[1] Department of Public Health and Infectious Diseases, Sapienza University, Rome, Italy
[2] Oncologic network, prevention and research Institute (ISPRO), Florence, Italy
[3] Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[4] Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy.
[5] Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[6] National Observatory on Smoking, Alcohol and Drugs, National Institute of Health, Rome, Italy
[7] Italian Society of Tobaccology (SITAB), Italy
[8] The COSMO-IT investigators in Appendix

Summary. The emergency caused by Covid-19 pandemic raised interest in studying lifestyles and comorbidities as important determinants of poor Covid-19 prognosis. Data on tobacco smoking, alcohol consumption and obesity are still limited, while no data are available on the role of e-cigarettes and heated tobacco products (HTP). To clarify the role of tobacco smoking and other lifestyle habits on COVID-19 severity and progression, we designed a longitudinal observational study titled COvid19 and SMOking in ITaly (COSMO-IT). About 30 Italian hospitals in North, Centre and South of Italy joined the study. Its main aims are: 1) to quantify the role of tobacco smoking and smoking cessation on the severity and progression of COVID-19 in hospitalized patients; 2) to compare smoking prevalence and severity of the disease in relation to smoking in hospitalized COVID-19 patients versus patients treated at home; 3) to quantify the association between other lifestyle factors, such as e-cigarette and HTP use, alcohol and obesity and the risk of unfavourable COVID-19 outcomes. Socio-demographic, lifestyle and medical history information will be gathered for around 3000 hospitalized and 700-1000 home-isolated, laboratory-confirmed, COVID-19 patients. Given the current absence of a vaccine against SARS-COV-2 and the lack of a specific treatment for COVID-19, prevention strategies are of extreme importance. This project, designed to highly contribute to the international scientific debate on the role of avoidable lifestyle habits on COVID-19 severity, will provide valuable epidemiological data in order to support important recommendations to prevent COVID-19 incidence, progression and mortality.

Key words: COVID-19, lifestyle habits, prognosis, SARS-COV-2, smoking, tobacco, risk factors.

Introduction

Italy was the first European country to be affected by COVID-19, an infectious disease caused by a new coronavirus named SARS-COV-2 (1). The infection started at the end of January 2020, rapidly spread, particularly in northern Italy, and almost 250,000 confirmed cases and more than 35,000 deaths (about 14% of all confirmed cases) occurred so far (July 28th).

Preliminary data showed that the main determinants of a poor prognosis of COVID19 were male sex, advanced age and previous comorbidities, most of which are tobacco-related diseases (2,3). In Italy, lethality rates vary between less than 1% for confirmed patients under age 50 years to over 25% for those aged 80 years or more (4). The risk of mortality in infected people increased with the increase in the number of concomitant chronic diseases, including in particular cardiovascular diseases (hypertension, ischemic heart disease, atrial fibrillation), diabetes, cancer, renal failure, and chronic obstructive pulmonary disease (2, 5).

Tobacco smoking appears to be an important avoidable risk factor for poor prognosis (2, 5-9), but its role on the development, progression, and prognosis of COVID-19 has not yet been fully clarified. Some studies found that, among patients with COVID-19, smokers had a substantial increased risk of major unfavourable health outcomes, including hospitalization in an intensive care unit, need for mechanical ventilation, or death (2, 5, 7-8, 10). Most of these studies, however, were based on relatively small samples or did not adjust for potential confounding factors. The role of smoking cessation on COVID-19 prognosis is also unclear, as former smokers in Chinese studies appeared to have a similar increased risk as current smokers. The role of e-cigarettes and heated tobacco products (HTP) on COVID-19 incidence and severity has not yet been investigated, but these products are likely to be associated with a poorer prognosis too (11).

Other lifestyle habits could be associated with COVID-19 progression and prognosis (12).

A French study showed a high frequency of obesity among patients admitted to intensive care units, with the disease severity increasing with increasing body mass index (13). No data on alcohol consumption and unfavourable progression of COVID-19 are currently available, but a direct association is possible due to alcohol-induced damage to the upper respiratory and digestive tract (14) and its weakening of the immune system, with an increasing risk of respiratory and pulmonary viral infections (15).

In addition, potential lifestyle factors associated with the setting where patients are treated, hospital versus home, have not yet been studied. Patients isolated at home, presumably with a less severe disease, might have different lifestyle habits compared to hospitalized ones. However, no data comparing lifestyle in the two settings of patients are currently available, and their ascertainment could explain some unresolved issues.

Further data from large, well-conducted studies, whose designs allow adjustment at least for age, sex and concomitant diseases are required.

Given the current absence of a vaccine against SARS-COV-2 and the lack of a specific treatment for COVID-19, to clearly elucidate if smoking, the most important avoidable risk factor, may have an important role on COVID-19 severity and prognosis, is of great importance for prevention strategies.

Thus, thanks to the close collaboration between the Italian Society of Tobaccology (SITAB), the Mario Negri Institute of Pharmacological Research (IRFMN) of Milan, the Institute for the Network of Prevention and Oncology Studies (ISPRO), the Sapienza University of Rome, and the request for original Italian data on these issues by the World Health Organization (WHO), the idea of organizing a multicentric study was born.

This study, with the acronym COSMO-IT (COvid19 and SMOking in ITaly), will enroll confirmed Italian cases of COVID-19 and its protocol is here presented.

Research Aims

The COSMO-IT study has three main objectives:

1) to quantify the role of tobacco smoking and smoking cessation on the severity and progression of COVID-19 in hospitalized patients;
2) to compare smoking prevalence and severity of the disease in relation to smoking in

hospitalized COVID-19 patients versus patients treated at home;
3) to quantify the association between other lifestyle factors, such as e-cigarette and HTP use, alcohol and obesity and the risk of an unfavorable outcome of COVID-19.

Materials and Methods

Study Design

COSMO-IT is a longitudinal observational study of confirmed COVID-19 patients. It will be prospective, for new patients, and retrospective for previously hospitalized or isolated patients.

Setting

About 30 hospitals in North, Centre and South of Italy joined the study. Among these, there are some large COVID units. Others are pneumology units, mainly coordinated by pneumologists belonging to the SITAB. Home dwellings of confirmed COVID-19 patients in selected territorial realities (e.g., centers of Tuscany and S. Marino) will be enrolled in the study too.

Patients

COSMO-IT will enroll, either retrospectively (from March to July 2020) or prospectively according to the approval dates of the various Ethics Committees, all consecutive, laboratory-confirmed COVID-19 patients admitted to the wards of the participating hospitals. Also, an opportunistic sample of consecutive, laboratory confirmed, COVID-19 patients isolated at their home, identified and followed by selected territorial realities on the same period will be enrolled in the study.

Experimental design

For research aim 1, the enrolled patients will be followed from the date at hospitalization to the date at discharge (or death). A "severe clinical course", defined as hospitalization in an intensive care unit, the need for mechanical ventilation or death versus a "mild clinical course", defined as use of oxygen or Continuous Positive Airway Pressure (CPAP) will be considered as a primary endpoint. The analysis of the data collected for this aim will allow to quantify the association between cigarette smoking and risk of severe versus mild clinical course of patients hospitalized for COVID-19. Moreover, the analysis of the association between time since stopping versus current smoking will enable the investigation of the effect of smoking cessation on COVID-19 severity and progression.

For research aim 2, COVID-19 patients with a disease confirmed by positive swab, who were isolated at their home, and identified in selected territorial realities will be enrolled. They will presumably have a milder clinical course and less serious symptoms compared with hospitalized patients. Similar set of data as those collected for hospitalized patients will be collected also for these patients. Comparing the two populations of patients in terms of smoking prevalence, we will be able to understand the role of tobacco smoking on hospitalization for COVID-19.

In the longitudinal study conducted in hospital centers, information will also be collected on some lifestyle habits for research aim 3. This study will allow us to quantify the association between these potential risk factors and the risk of severe COVID-19 clinical course.

Data collection

For each patient enrolled in the study (either hospitalized or isolated at home), data on socio-demographic characteristics, major pre-existing chronic conditions and prior use of selected drugs will be collected. In particular, information will be gathered on anthropometric characteristics (current self-reported weight and height) and selected lifestyle habits, including tobacco smoking (e.g., smoking status, and, for former smokers, time since stopping), e-cigarette and HTP use, and consumption of alcoholic beverages at the time of hospitalization or isolation at home. Also, information on COVID-19 symptoms, onset date and severity of the disease will also be collected. For hospitalized

patients, information will be collected on the type of hospitalization, type of therapy, prescribed drugs and possible complications during hospitalization. For patients isolated at home, relevant information of the clinical course will be collected. At the end of the hospitalization (or the end of the clinical course for patients in home isolation), the outcome will be recorded (i.e., discharge or laboratory confirmed recovery, any transfer and death).

Baseline and follow-up information will be collected prospectively, for new patients, or retrospectively for previously hospitalized or isolated patients extracting data already available on the patient's medical records or by contacting patients (or relatives, in the case of deceased patients) to collect missing information. All data will be collected through an electronic data collection form by the researchers at each center, and provided anonymously to the IRFMN, where data will be managed in accordance with the current European privacy laws.

Statistical analysis

Data will be summarized through appropriate descriptive statistics. Analyses of main and secondary outcomes will be done through multivariable analyses. In particular, logistic regression models will be used to quantify the association between selected potential risk factors and the risk of COVID-19 severity and prognosis, after allowance for several covariates, including sex, age and prior comorbidities.

Sample size

As a primary endpoint, we will consider a "severe clinical course" (defined as hospitalization in an intensive care unit, the need for mechanical ventilation or death) versus a "mild clinical course" (defined as use of oxygen or CPAP). An average of 100 patients are expected to be enrolled in each of the 33 Italian hospital centers. Assuming a smoking prevalence among patients with a mild clinical course of 20%, a sample size of 3000 COVID-19 patients (including about 15% with a severe clinical course) will allow to appreciate a significant odds ratio (OR) for smokers versus non-smokers of at least 1.35, with alpha = 0.05 and power = 0.80. For the group of COVID-19 patients isolated at their home and enrolled by the territorial units, a sample size of about 700-1000 patients is expected to participate in the study.

Coordination centers

IRFMN and ISPRO will be the coordination centers.

Ethical aspects

This study protocol has been approved by the ISPRO Ethics Committee on June the 6th 2020 (N. 17495), which acts as the Coordinator of Ethical Issues. It has now been submitted to the Ethics Committee of each data collection center. Each patient will receive all the details of the study and will be contacted to give an informed consent. In case of deceased patients, the informed consent will be asked to a familiar or close relative.

Limitations

One of the main problems is the long period of time needed to deal with the ethical aspects of each of the participating hospitals.

Another problem concerns the possibility that not all the information on the lifestyle habits will be available from the medical records. For this reason, we planned to contact patients and interview them about their lifestyles. This can lead to some difficulties, particularly for deceased people; in this case, informed consent and missing data will be requested to a family member or close relative.

Significance and Innovation

This project is designed to highly contribute to the international scientific debate on the role of lifestyle habits on COVID-19 severity. Indeed, scientific knowledge on the possible role of major risk factors (including tobacco, HTP, obesity and alcohol) on COVID-19 outcomes is still limited.

The present study, the first in Italy based on a large multicenter sample, will be able to quantify the association between several avoidable lifestyles and the risk of complications in COVID-19 prognosis. These findings will have significant implications from a public health perspective and a substantial impact on the National Health System, particularly in the current absence of a vaccine or an effective treatment for COVID-19 because they will provide correct recommendations to prevent COVID-19 incidence, progression and mortality. The findings of this study will be disseminated via peer-reviewed publications and presentations at national and international conferences.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

APPENDIX: The COSMO-IT Investigators

Ancona, Ospedali Riuniti di Torrette di Ancona (Federico Giulietti, Riccardo Sarzani, Francesco Spannella)

Benevento, AORN "S.Pio"- P.O. "G.Rummo" (Mario Del Donno, Stefania Tartaglione)

Catanzaro, Policlinico Universitario Magna Graecia, AO Mater Domini (Giuseppina Marrazzo, Girolamo Pelaia)

Eboli (SA), Ospedale Eboli (Vincenzo D'Agosto)

Firenze, ARS Toscana (Alice Berti, Fabio Voller)

Firenze, Azienda Ospedaliera Universitaria Careggi (Salvatore Cardellicchio, Chiara Cresci)

Firenze, Istituto per lo Studio, la Prevenzione, e la Rete Oncologica (Giulia Carreras, Giuseppe Gorini)

Foggia, Policlinico Riuniti (Maria Pia Foschino Barbaro)

Genova, Policlinico S. Martino (Raffaele De Palma, Simone Negrini, Vera Sicbaldi)

Imperia, Ospedale di Imperia, ASL 1 Imperiese (Antonella Serafini)

Lecce, Ospedale Vito Fazzi (Mario Bisconti, Leonida Refolo)

Milano, Fondazione IRCCS Istituto Nazionale dei Tumori (Roberto Boffi, Chiara Veronese)

Milano, Istituto di Ricerche Farmacologiche Mario Negri IRCCS (Cristina Bosetti, Silvano Gallus, Alessandra Lugo, Claudia Santucci, Chiara Stival)

Milano, Ospedale San Raffaele (Giovanni Landoni, Patrizia Rovere, Giulia Veronesi)

Monza, Ospedale San Gerardo (Paola Faverio, Werner Garavello, Alberto Pesci)

Napoli, A.O.R.N. A. Cardarelli (Raffaella Giacobbe, Paola Martucci)

Napoli, Ospedale Domenico Cotugno (Roberto Parrella, Francesco Scarano)

Parma, Azienda Ospedaliero Universitaria di Parma (Marina Aiello, Alfredo Chetta)

Piacenza, Ospedale Guglielmo da Saliceto (Cosimo Franco, Angelo Mangia)

Pisa, Azienda Ospedaliero-Universitaria Pisana (Laura Carrozzi, Fabrizio Maggi, Fabio Monzani, Francesco Pistelli, Patrizia Russo)

Pistoia, Ospedale San Jacopo, Azienda USL Toscana Centro (Antonio Sanna)

Reggio Calabria, Grande Ospedale Metropolitano (Filippo Maria Barreca)

Repubblica di San Marino, Ospedale di Stato (Valentina Conti, Enrico Rossi, Mei Ruli, Silvana Ruli)

Rieti, Ospedale S. Camillo De Lellis (Shokoofe Eslami Varzaneh)

Roma, Istituto Superiore di Sanità (Roberta Pacifici)

Roma, Azienda Ospedaliera San Camillo Forlanini (Rosastella Principe, Simone Guerrini, Alfredo Sebastiani, Giovanni Galluccio)

Roma, Azienda Ospedaliero-Universitaria Sant'Andrea (Aldo Pezzuto, Alberto Ricci)

Roma, Azienda Ospedaliero-Universitaria Policlinico Umberto I (Elena Casali, Claudio Mastroianni)

Roma, La Sapienza Università di Roma (Maria Sofia Cattaruzza)

Sassari, Azienda Ospedaliero Universitaria di Sassari (Pietro Pirina, Francesca Polo)

SITAB Società Italiana di Tabaccologia, Italy (Vincenzo Zagà)

Torino, Ospedale San Giovanni Bosco, ASL Città di Torino (Fabio Beatrice)

Treviso, Ospedale Cà Foncello, ULSS 2 (Micaela Romagnoli)

Udine, Azienza Sanitaria Universitaria Friuli Centrale (Massimo Baraldo, Pier Giorgio Cojutti, Elena Graziano, Davide Pecori, Carlo Tascini)

Vimercate (MB), ASST Vimercate (Biagio Tinghino)

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Correspondence:Maria Sofia Cattaruzza
Department of Public Health and Infectious Diseases,
Piazzale Aldo Moro 5
Sapienza University
00185 Rome, Italy
e-mail: mariasofia.cattaruzza@uniroma1.it