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Pharmacological Overtreatment and COVID-19 Deaths: Analysis of Comorbidity Data on the Elderly Population in Italy

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ABSTRACT

This article invites to further investigate the link between pharmacological overtreatment and COVID-19 related deaths in the elderly population. Unhealthy diets and environmental pollution negatively affect the gastrointestinal system leading to complications such as metabolic dysfunctions, hypercholesterolemia, obesity, and microbiota dysbiosis. Such complications are important factors in explaining COVID-19 mortality in the elderly population. As highlighted by the Italian case, another important source of those complications is pharmacological overtreatment. This article analyses COVID-19 related comorbidity data in Italy by comparing data from selected Italian, American and Chinese case studies.

The gastrointestinal system is involved in Covid-19 due to the high presence of ACE-2 receptors and interactions with the Microbiota genome. Obesity induces a flattening of intestinal bacterial varieties and a rigidity of lipid cells' membranes. In the US, obesity in over 65 was present in almost all deceased patients. Environmental pollution alters the body mineral system. In China, gastrointestinal symptoms were present in over 50% of patients. Older adults are more likely to suffer from long-lasting chronic diseases that break cell homeostasis on different functional levels. The co-occurrence of multiple pathologies often leads to pharmacological overtreatment, especially in the elderly. In Italy in particular, where most COVID-19 deaths were among the elderly, comorbidities are correlated with pharmacological overtreatment. Multiple drug prescriptions weaken the immune system and compromise the gastrointestinal system, perversely reinforcing the patient's dependency on further drug prescriptions with the related toxic metabolic interactions.

This article highlights pharmacological overtreatment as an important area of investigation for studies assessing the impact of comorbidities in COVID-19 deaths, and for further research into effective COVID-19 treatment in the elderly.

Keywords: Overtreatment, Obesity, Metabolic Dysfunction, Microbiome, Western food, Environmental Pollution

INTRODUCTION

Research on COVID-19 at first relied on anecdotal evidence, then increasingly on statistical analyses as data gradually started to flow in. Lacking reliable data and pressured by the scale and urgency of the crisis, research efforts on tackling COVID-19 have been characterized by several turning points, especially during the early stages of the crisis. One of these turning points was a medical discovery made in Italy in April 2020. A group of medical doctors in Bergamo and Milan performed 38 autopsies demonstrating a disseminated intravascular coagulopathy (DIC) and diffuse thrombosis of peripheral vessels. [(1)] Thrombus pulmonary embolism is however not cured with oxygen. The discovery was confirmed in Germany in May 2020 by a Prospective Cohort Study on 12 autopsies. [(2)] Acute Respiratory Distress syndrome (ARDS) therapy with its oxygen

treatment was therefore wrong. Since then, therapies all over the world have adopted protocols based on heparin with positive results in terms of healed patients. [3-4]

Nevertheless, the scale of increasing hospitalizations quickly shifted the focus on early intervention at the first symptoms. Despite the controversy on the effectiveness of hydroxychloroquine treatments, data from Asia [5] and France [6] seemed to confirm that they could reduce the severity of the disease when applied at the beginning of the disease. This occurred also in my personal experience in March 2020 with chloroquine in combination with Zinc. [7] Antivirals and monoclonal antibodies were also later found to help prevent a more severe evolution. Hydroxychloroquine treatments were eventually cleared from controversy in June 2020, when the Surgisphere review casting doubts on their effectiveness was eventually discredited. [8]

Early intervention at the first symptoms is particularly crucial for older patients affected by comorbidities. A high mortality rate associated with the presence of commodities was already emerging from the first reports: the majority of fatalities were recorded among the over-65s and associated with pre-existing diseases. The over-65s with comorbidities were almost immediately identified as the most vulnerable group among COVID-19 patients, especially over 80 years.

MATERIALS

Comorbidities are a structural co-cause in the majority of Covid-19 related fatalities. Data on mortality from China, United States and Italy also show that such comorbidities were often associated with metabolic dysfunctions, highlighting the centrality of the gastrointestinal system in the patient's response to the disease. The gastrointestinal tract is relevant in particular for the presence of ACE-2 receptors. These receptors act as doorways for COVID-19 to get into the organism's cells. COVID-19's SARS-CoV-2 proteins link to those receptors, especially in the lungs' and intestines' cells. Environmental pollution and unhealthy diets with the associated metabolic dysfunctions were quickly identified as main aggravating factors in COVID-19 recoveries. Environmental pollution produces endocrine disruptors that alter cellular homeostasis and cause metabolic diseases and cellular degenerations. [9] The higher incidence of COVID-19 deaths in North Italy as compared to the less air polluted regions in the South seems to confirm environmental pollution as a relevant aggravating factor. [10]

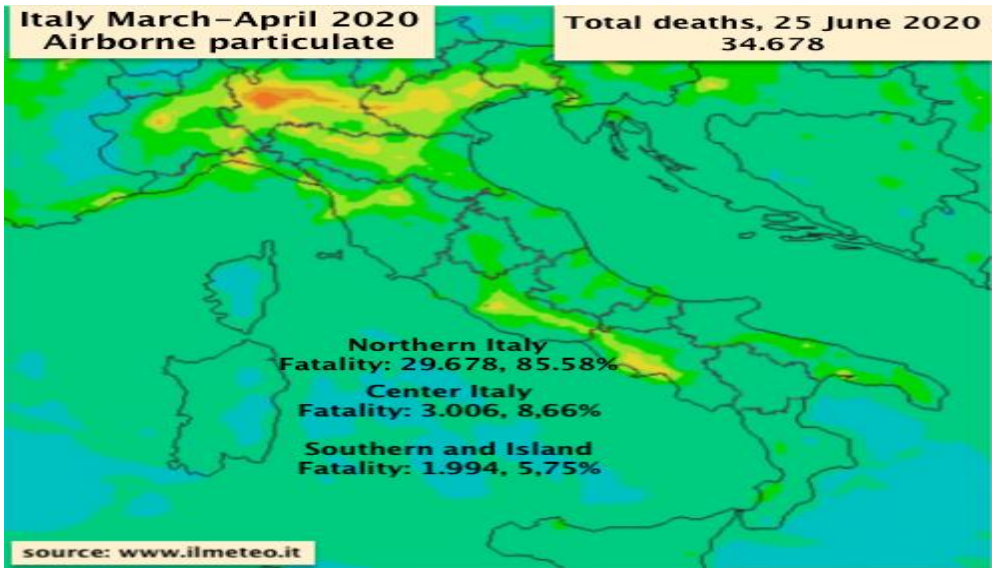

Figure 1: The image above represents the geographical distribution of air pollution on the Italian peninsula. It is evident a correlation between air pollution levels and different mortality rates. Out of 34,678 deaths, 85.58% occurred in the north, 8.66% in the center and 5.75% in the south of the country.

In China's Hubei Region, the Cross-Sectional Multicenter Study reported that 21.6% patients (median age: 53) had cardiovascular diseases, 11.8% endocrine system diseases, 4.4% respiratory diseases, 6.3%, malignant tumors. 50.5% of patients had symptoms that could be divided into three categories: 1) generic flu syndrome: fever, headaches, conjunctivitis, chills, and muscle pains. 2) lung symptoms: dry cough, sore throat, breathing difficulties, shortness of breath, chest pain, loss of speech, or movement. 3) gastrointestinal symptoms (GI): loss of taste or smell, nausea, vomiting, diarrhea, lack of appetite, abdominal pain, skin rash, discoloration of fingers or toes. Fatigue, weakness, and lack of appetite are constantly present. [(11)] Unhealthy diets produce negative effects on patients' metabolism, immune system, cognitive state as well as protection against pathogens. [(12)] The composition of the intestinal microbiota is strongly influenced by dietary patterns. The western processed diet - rich in fats and sugars but poor in raw fibers - increases the Firmicutes at the expense of Bacterioids. The fecal microbiota of children living in Burkina Faso, Africa, compared to that of children from Florence, Italy, shows that the African feces contained higher amounts of Bacterioids and lower quantities of Firmicutes. [(13)]

Within the New York City area, the most common comorbidities among its 5700 hospitalized patients (median age: 63) were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%). This report considered obesity as a new comorbidity: the 41.7% referred to 1st and 2nd grade obesity (BMI≥30) is increased by 19% for pathological obesity (BMI≥35). Another 31% can be added by official American data (overweight BMI below 29). The sum of these data shows an excessive accumulation of fat in 91% of the elderly population. [(14)]

Metabolic dysfunctions are also frequently correlated with abuse of drugs, toxic adverse reactions to drugs and medical errors in prescribing drugs. Pharmacological overtreatment as an aggravating factor has received less attention as compared to environmental pollution and unhealthy diets but appears to be particularly relevant in the Italian case. Italians are the oldest population in Europe, but with a high consumption of drugs which increases every year.

In Italy's Northern Lombardy Region, 68% of its 1591 patients (median age: 63) had more than one pathology when admitted to ICU: hypertension 49%, cardiovascular disease 21%, hypercholesterolemia 18% and only 4% had chronic obstructive pulmonary disease COPD. [(15)]

Table 1: Pre-existing chronic pathologies present a uniform "metabolic dysfunction syndrome" in the Asian, American and European continents.

ITALY*		UNITED STATES, NY**	CHINA, HUBEI		
Age median	63	63	52,91		
Sex M/F	82%/18%	60,3%/39,7%	52,45%/47,45		
CFR§	13,97%	6,01%	5,52%		
All				Without GI§§	With GI§§
Hypertension 67.9%		Hypertension 56.6%	Cardiovascular disease 21,57%	20,79%	22,3%
Ischemic heart disease 22.1%		Obesity BMI≥30 41%	Endocrine disease 11,76%	13,86%	9,71%
Atrial Fibrillation 21.6%		Morbid Obesity BMI≥35 19%	Malignancy 6,37%	4,95	7,77
Diabetes 30%		Diabetes 33.8%	Respiratory disease 4,41%	1,98%	6,8%
Malignancy 15.8%		Asthma 9%	Digestive disease 3,34%	2,97%	3,88%
COPD 18%		Coronary artery disease 11,1%	Nervous disease 2,45%	3,98%	0,97%
Diarrhea 6%		Congestive heart failure 6,9%			
Obesity 11%		COPD 5,4%			

Legend: **ISS - Ministry of Health Italy. Other disease: Heart failure, Stroke, Dementia, Chronic liver and kidney disease, Dialysis, Respiratory failure, HIV and Autoimmune diseases. Hypercholesterolemia is not reported. 16% of patients followed ACE-inhibitor. **US reported also HIV, Obstructive sleep apnea, Cirrhosis, Hepatitis C and B.§Case Fatality Rate. §§Gastrointestinal symptoms*

The report of the Italian Drugs Agency (AIFA) on OsMed 2018 points out that 98% of over-65s take more than 3 doses of drugs every day. On average, 6.7 different substances are supplied free of charge by the National Health Service with

a progressive increase in active ingredients by age. 22% of over-65s take 10 active ingredients at the same time. Consumption increases every year with age reaching a maximum in the 80-84 age group. An overtreatment of 7 active ingredients/day generates adverse drug reactions in senior patients, with undesirable effects often underestimated by primary care physicians. [(16)] In 2015 an OREDIA study observed 3,700 diabetic patients and confirmed the presence of overtreatment in vulnerable populations. The mean age was 81, body mass index was ≥29; 96% patients had hypertension, 78% dyslipidemia with associated cardiovascular risk factor. Most patients were on multiple concomitant therapies, primarily represented by anti-hypertensive (95.5%: one/two RAAS blockers in 74.2%), lipid-lowering (74.5%) and anti-platelet agents (64.8%). The mean number of co-medications was 5.5±2.8. [(17)] However, the survey on socio-demographic characteristics, smoking habits and alcohol consumption, also confirmed other risk factors such as hypertension, diabetes and obesity. [(18)] The Italian Ministry of Health reported 3.3 as the average number of comorbidities out of the total number of deceased patients in the first four months of 2020: 59.5% had three or more underlying diseases, 21.5% had two diseases, 14,9% had a single disease and only 4.1% had no diseases. In 92.3% of hospitalized patients the most common symptoms were fever, dyspnea, cough, hemoptysis and diarrhea - cholecystitis, perforation of the intestine, intestinal obstruction, cirrhosis were also present, but less commonly observed. Deaths under the age of 50 represent only 1.1% out of 32,938 fatalities. Such 1.1% consisted of 366 patients of which 62 had serious pre-existing pathologies (cardiovascular, renal, psychiatric pathologies, diabetes, obesity) and only 14 had no major pathologies. [(19)]

DISCUSSION

Pharmacological overtreatment is a prevalent feature of the Italian case. Especially the over-80-85s are recipients of multiple drug prescriptions with different active ingredients affecting the metabolic system. The editorial "Improving Quality by doing Less" highlights that metabolic dysfunctions related to COVID-19 are on top of the overtreatment list. [(20)] The role played by drug–drug or drug–disease interactions, and medical errors in designing drug prescriptions in COVID-19 patients is a research area that needs further exploring. The attention should be placed not only on single classes of drugs, but also on the iatrogenic interactions that originate from exposure to multiple active ingredients. Within this area, how pharmacological overtreatment may affect ACE-2 receptors – i.e. COVID-19's doorways into cells – is a research question of particular relevance.

CONCLUSION

The implications of comorbidities have not been fully investigated. Cellular metabolic dysfunctions, which get worse over time because of the related innumerable artificial chemical toxicities involved, play a key role in deciding between life and death in Covid-19. [(21-22)]

Elderly population's health protection could be improved by imposing WHO recommendations on reducing toxins from processed foods and environmental contamination of soil, water, air and diet by agri-food-pharmaceutical system. Adding to those challenges, pharmacological toxicity is another major problem that needs to be fully addressed for the same purpose.

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