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Clinical Insights

Predicting adverse outcomes in patients with COVID-19: just an epidemiological debate or a valuable clinical approach?

On February 16, 2020 the executive committee of the European Federation of Internal Medicine (EFIM) met in Malaga, Spain, to prepare for the EFIM annual congress to be held in March 2021. As usual, it was a very pleasant and fruitful meeting, which allowed us to meet face-to-face, work hard and enjoy the company and the city. Less than a week later, Prof. Nicola Montano, from Milan (Italy), the president of the EFIM at that time, warned the EFIM executive committee members of the alarming outbreak of the SARS-CoV-2 pandemic in Lombardy.

Just a few days later, on February 25, 2020, the first patient with COVID-19 was diagnosed in Barcelona, Spain, the city where I live and work, and on March 7, the first patient was admitted to my hospital. Deeply concerned by the spread of the disease and its severity, the other members of the EFIM executive committee, Drs. Dror Dicker (Tel Aviv, Israel), Runólfur Pálsson (Reykjavík, Iceland), Valentin Kokorin (Moscow, Russian Federation), Ricardo Gómez-Huelgas (Malaga, Spain) and Mrs. Aneta Trajkovska (Brussels, Belgium), waited in shock to hear the news from Milan and Barcelona, as well as of the arrival of the pandemic in their respective countries.

The world quickly entered a situation of global crisis and health emergency, and the WHO declared that COVID-19 was a pandemic on March 11, 2020 [1]. As worrying as this statement was, no one could have predicted how events would unfold in the ensuing months and the suffering that that would entail.

Suddenly, our clinical practice based on modern medicine was called into question and went back in time. We returned to practicing medicine on a case-by-case basis, without guidelines or standardized practices, and without any help from our current popular advisors "Dr. UpToDate" and "Dr. Google". Our decision-making abruptly ceased to be supported by evidence from large cohort studies or multicenter randomized clinical trials (RCTs). Bedside observations and the experience we accumulated in the treatment of individual patients were the only pillars of information to improve our care practice. Medicine was once again on a war footing, focused on urgent care and saving lives. Worryingly, despite living in a fully connected world, we have had great difficulty in relating epidemiology to clinical practice. Notwithstanding the lack of time and resources, the progressive aloofness between clinicians and epidemiologists over decades explains our inability to obtain solid and rapid evidence on the prediction of poor outcomes and mortality in COVID-19.

As a result, inaccurate news about the infection emerged from the early days of the pandemic. In a globalized world, in a climate of immediacy, social media, and the pressure of medical journals to publish quickly, a disturbing volume of information has been generated in the scientific literature [2]. In this regard, the COVID-19 pandemic has produced three relevant innovations never seen before. To begin with, for the first time in history, hundreds of journals and publishers decided to openly publish all works dealing with any aspect related to COVID-19 or SARS-CoV-2. Secondly, medicine in all its disciplines, religiously began to use prepublications on specific servers prior to a peer review process — at the end of September 2021 there are about 15,848 COVID-19 preprints in medRxiv and 5,840 in bioRxiv. Finally, "live" systematic reviews (with meta-analyses) that are constantly updated, unlike conventional ones, which have a deadline for the available data, became the norm.

Unfortunately, the only available initial sources of evidence were the significant number of small-sample, non-controlled retrospective observational studies published by predatory journals or that fed the preprinted databases. This created a lot of confusion in an emergency situation where the general tendency is to accept any news as good, even if it is not well founded. Among the negative consequences, there has been a generalization of unproven practices, not free of adverse effects, as part of the routine care of tens of thousands of patients worldwide.

In terms of control and prevention, we [*clinicians and epidemiologists*] have collectively reacted late to address the entire population and not just the patient facing us. It has therefore taken us a long time to properly investigate the epidemiology of this new complex disease, based on the really relevant questions that physicians have been asking from the frontline. This has made it even more difficult for international health authorities and regulatory agencies to make the right decisions, in a timely manner, and to strengthen good practices with a sufficient level of quality for standardization.

Regrettably, specialists in internal medicine, pulmonology, infectious diseases, microbiology, immunology, and emergency and intensive care, have long disagreed on how to deal with the disease, and have repeated mistakes made in the past in other pandemics like when AIDS broke out. From that experience, we should have learned how to investigate a communicable disease by all possible clinical and epidemiological means [3]. From 1981 onwards in the United States, there was an increased incidence of Kaposi's sarcoma and pneumonia due to Pneumocystis carinii in gay men. A year later, the same phenomenon was observed in hemophiliacs and in individuals who had received multiple transfusions. As with the current COVID-19 pandemic, a large number of unconnected clinical and epidemiological studies, aimed at describing the variables of the disease and studying the

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possible prognostic factors associated with it, producing an exceptional amount of information in a very short period of time. Eager to investigate the disease in all its facets, interest was focused on the group of those most affected, namely, male homosexuals. Many studies found significant differences depending on type of sexual practice and other variables. Some studies initially concluded that heterosexual contact was not a good means of transmitting AIDS. This claim was called into question when clinicians reported a number of AIDS cases in Central Africa, noting virtually the same frequency of the disease in men and women. It was from then on that it was recognized that AIDS transmission could occur through both homosexual and heterosexual contact. Regardless of the social implications of this dramatic discovery of a new pathway for the transmission of AIDS (not to mention the unfair journalistic definition of the "homosexual plague" and the consequent criminalization of homosexuality), this led to a delay in dissemination of correct information in predicting adverse outcomes in patients with AIDS.

The same question which previously arose with AIDS now arises with COVID-19, about whether the disease should be addressed from an epidemiological or a clinical standpoint. History shows that the clinical-epidemiological approach was not used in a comprehensive way in either case: errors in information gathering of different variables and the concentration of observers and researchers in certain countries and from certain populations, have undoubtedly affected the research process, leading to biases and errors.

An embarrassing example of this in the media, was the football league type comparison of the number of cases and deaths by country. From an epidemiological perspective, we know that these comparisons are subject to significant biases. The number of cases and deaths reported depends, among other things, on the availability of diagnostic tests in each country or criteria for reporting deaths.

In the face of fake news and reckless assertions, the responsibility of high-impact journals as reliable sources of scientific evidence has become more valued than ever. Even today, there is insufficient available data on the effectiveness of some drug regimens to treat the most severe COVID-19 patients. While it is understandable that, in the absence of approved alternatives, the physician uses experimental drugs in the case of a seriously ill patient, clinicians and epidemiologists have a duty to critically reflect on some decisions made during the pandemic. Too often, physicians have irresponsibly administered drugs based only on in vitro studies, highly dubious published small series without a control group, and RCTs with inappropriate enrollment criteria or an insufficient sample.

Collective despair reached the surprising point that, even with low-quality evidence, international agencies' regulatory references initially agreed to authorize exceptional ways to use certain drugs, despite ethical issues regarding serious adverse effects they might have [4]. Among the most unfortunate and well-known examples has been the use of hydroxychloroquine or lopinavir-ritonavir [5,6]. While waiting for RCTs, the initial natural tendency of observational studies was to attribute favorable results to these drugs when patients were cured, and to the disease when the evolution was unfavorable. However, in June 2020, the WHO announced the discontinuation of the hydroxychloroquine and lopinavir/ritonavir arms of the Solidarity trial [7]. The decision was based on evidence from the Solidarity trial, the UK's Recovery trial and a Cochrane review of all trials available, showing that hydroxychloroquine vs. standard-of-care and lopinavir/ritonavir vs. standard-of-care did not reduce adverse outcomes in hospitalized patients. Worryingly, taking hydroxychloroquine or lopinavir/ritonavir increased the risk of heart rhythm problems, blood and lymph disorders, kidney injury or liver failure in COVID-19 patients.

Although later than we would have liked, the positive consequence of facing such extreme adversity is that it has been the trigger for regaining trust between clinicians and epidemiologists, to work together on the common goal of improving clinical care. In essence, the healthcare community has gradually come to realize that, based on clinical observations and the comparison of groups, epidemiology can help us better understand the risk of disease or the risk of suffering from a poor prognosis, when falling ill, and/or receiving certain treatments. Furthermore, after the first few months of chaos and shock, we have also realized that, with a thorough knowledge of epidemiology, doctors can take better informed decisions. This is precisely what defines clinical epidemiology.

The concept of "clinical epidemiology" first emerged in 1938, in a presidential speech to the American Society of Clinical Investigation made by Prof. John R. Paul, from the Department of Internal Medicine at Yale University School of Medicine [8]. Clinical epidemiology is defined as a critical way of thinking that goes beyond the doctor-patient encounter. It is from a clinical observation that one wonders why and how the person became ill. It is our responses to such questions that will serve to control and prevent this same disease in many other potential patients. Clinical epidemiology developed significantly in the second half of the twentieth century; however, it was the analysis of the cholera epidemic in London by Dr. John Snow, in the middle of the nineteenth century, which probably established the original practice of what would subsequently be named "clinical epidemiology" [9]. Dr. Snow, who is considered the father of modern epidemiology, applied epidemiological methods while providing direct care to patients. He checked to see whether cases were grouped in areas where the water consumed was contaminated, and mapped the water wells in the district of Soho. By locating the heart of the epidemic, he improved not only the health of his patients but also public health at a population level.

An epidemiological approach clearly works well when used hand in hand with clinicians. Although "orthodox" epidemiologists have to deal with large groups of people, it is the multiplication of clinical observations that gives them results. If epidemiology does not start from clinical observations, it runs the risk of its findings being disseminated, but without being truly applicable and effective. It is the clinician, due to their daily contact with patients and problems, who is best placed to generate the most interesting questions and hypotheses. At the same tisssme, in addition to thinking as a medic, physicians should be educated and willing to think epidemiologically and work in collaboration with epidemiologists.

In a health emergency situation like the COVID-19 pandemic, the lesson for clinicians and epidemiologists is clear: evidence-based medicine must continue to be practiced, in collaboration, even in desperate situations. Although front-line physicians have justified taking decisions knowing that evidence is scarce, such scarcity of proof should never be grounds for decision-making.

Therefore, there is an urgent need to develop learning-based systems and big data analytics that serve to reconcile and recover the integration of real-world observations from clinical practice with high-quality epidemiological research. Only from a clinical-epidemiological collaborative approach, can we efficiently achieve the mutual objective of defining a new disease, identifying its cause, its variables and their distribution, and establishing guidelines for its control, treatment and prevention. This insight is probably one of the great legacies left to us by the current pandemic.

Declaration of Competing Interest

I declare that no conflict of interest exists.

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