Almanaq International Publications

Gazette of Pharmacology and Clinical Research

Mini Review Open Access

The value of real-world evidence for clinicians and clinical researchers in the coronavirus crisis

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Received: April 23, 2020; **Accepted:** June 16, 2020; **Published:** June 30, 2020

Abstract

In the midst of a rapidly spreading global pandemic, real-world evidence can offer invaluable insight into the most promising treatments, risk factors, and not only predict but suggest how to improve outcomes. Despite overwhelming news coverage, significant knowledge gaps regarding COVID-19 persist. The current uncertainties regarding incidence and the case fatality rate can only be addressed by widespread testing. But the paucity of testing, and diversity of approaches implemented in different countries, particularly among the general asymptomatic public, perpetuates a lack of understanding about spread and infectivity. The essential indicators that would describe the pandemic more accurately can be obtained using real-world data (RWD). To that purpose, we designed a data collection tool to collect data from hospitals that treat COVID-19 patients. The captured data will enhance our understanding of the COVID-19 pandemic, identify risk factors relevant for triage, relate to other similar seasonal infections and gain insight into the safety and efficacy of experimental and off-label therapies. Knowledge derived from a focused data collection effort will enable clinicians to adjust rapidly clinical protocols and discontinue interventions that turn out to be ineffective or harmful. By deploying our elegantly designed survey to capture routine clinical indicators, we avoid placing an additional burden on practitioners. Systematically generating real-world evidence can decrease the time to insight compared to randomized clinical trials, improving the odds for patients in rapidly changing conditions.

Value of Real-World Evidence in the Coronavirus Crisis

The gold standard for studying efficacy and safety of a treatment is the randomized controlled clinical trial. In this experimental setting, a highly select and homogenous population is studied and the pattern of treatment and follow up is fixed. But if the inclusion and exclusion criteria are too restrictive, it may be impossible to generalize the conclusions to the broader population. Real-world data provide complementary evidence to randomized controlled trials by providing insight into effectiveness under actual conditions in a diverse and heterogeneous patient population. In actual clinical practice, physicians may employ a variety of therapeutic regimens or interventions that may change depending on clinical judgment. Real-world data generated during the course of care and may be mined from such diverse sources as electronic medical records and billing claims to surveys, wearables, and data collected from medical devices during care delivery. Electronic medical records enable research through access to a wealth of clinical data from regular practice.

Covid-19 is a reminder of how much the healthcare sector relies on innovation and real-life, real-time feedback to offer faster, safer, more effective treatments to address the challenges posed by a new disease where new observations emerge daily. Randomized clinical trials take time to design, approve, recruit, and perform, and by the time they are underway, their approach may be obsolete. In a rapidly spreading pandemic caused by a previously unknown disease, real-world data becomes an indispensable knowledge component in medical practice. The use of real-world data in the control of infectious diseases is hardly a new concept. The Global Epidemic and Mobility Project (GLEAM) has combined disease transmission models and data on populations and mobility to develop strategies to combat tropical diseases. The platform was employed to model the Ebola outbreak in West Africa, Zika in the Americas, and the 2009 H1N1 global flu pandemic [1].

Product and disease registries are an excellent source of real-world data that can provide high-quality, structured information for analysis. To combine the best practices from the design of clinical trials and to achieve the flexibility of real-world data sourcing approaches, we created a survey tool to populate a specialized registry. To accommodate all the necessary changes of monitored parameters and adjustments to therapeutic regimens, we are able to add variables to our survey without modifying questions and changing analytical outputs. This approach allows visualization of partial results shortly after participating hospitals enter their data.

Data Collection: What is being done so far and how it falls short

Numerous efforts have been undertaken by authoritative organizations and institutions around the globe during the current coronavirus pandemic, but their methodologies of selecting patients for testing, the choice of tests, and reporting criteria vary from country to country. Even the most commonly cited sources, the WHO, The Johns Hopkins Bloomberg School of Public Health and Worldometer, report cumulative numbers of detected

cases and deaths rather than standard epidemiological indicators such as incidence and prevalence, the number of infected per 100,000, number of hospitalizations per 100,000 or case fatality risk [2][3][4]. These indicators are not yet available because they are dependent on the standardization of testing. Moreover, thresholds for hospitalization vary significantly among countries and regions, so significant uncertainty remains with regards to the percentage of hospitalized patients who require critical care.

Even when standard epidemiological indicators have been attempted, they are piecemeal, incomplete and unconnected. E.g., in Germany physicians report COVID-19 cases into a national database maintained by the Robert Koch Institute [5]. According to this source, the highest incidence was reported in the German states of Hamburg and Bavaria, approximately 126 cases per 100,000. About 86% of the 732 reported deaths to date (April 1, 2020) occurred in persons aged 70 years or older. Germany performs about 50,000 tests a day [6].

A sampling of other tracking:

- Iceland shows an incidence of about 1%, based on 220 confirmed cases out of 2,278 samples taken at Landspítali hospital [7].
- In the UK, a widely publicized and debated Oxford study suggests most cases are asymptomatic and that nearly half of the UK population has already been infected. [8][9].
- Based upon published reports thus far, epidemiologist John Ioannidis from Stanford University School of Medicine places the COVID-19 death rate anywhere between 50 and 1000 per 100,000 [10].

While these reports attempt to define the magnitude of the epidemic, they produce no actionable information, only overwhelming news coverage that frightens the public rather than conveys hope**.**

Regarding effect of testing on epidemiological indicators:

Only widespread testing can answer the question of incidence and death rate. Until that occurs, there is reliance on tests performed upon hospitalizations, resulting in a highly biased sample of severe cases.

- The small Italian town of Vò is an example of a timely, well-managed initiative to test the entire population and stop the spread of the disease. The University of Padua, in collaboration with the Veneto Region and the Red Cross, tested all 3,300 inhabitants in response to their first COVID-19 fatality. They found ninety positive cases, of which six were asymptomatic. Therefore, the researchers were able to contain the infection by isolating all people who tested positive [11].
- The Financial Times, citing the Oxford study, argue that the reason for this uncertainty about the COVID-19 death rate is the biased sample of people tested: Only the most severe cases are identified as positives, while the majority of cases are mild or asymptomatic [9].

This paucity of testing, particularly among the general asymptomatic public, perpetuates lack of understanding about spread and infectivity. Testing an entire population to detect mild and asymptomatic cases and silent spreaders is not feasible, partly due to the limited availability of tests, their often-problematic sensitivity and reliability and also inevitable prioritization of clinically relevant cases.

The Centre of Mathematical Modeling of Infectious Diseases (CMMID) estimated under-reporting by using a delay-adjusted case fatality ratio estimate as available from the European Centre for Disease Prevention and Control (ECDC). They argue that the delay between case creation (positive test) and fatal outcome leads to a bias in the estimate of the case fatality ratio.

The authors used an adjustment of 13 days (SD 12.7 days) for this delay. They calculated the delay from the time lag between the date of hospitalization and date of death. The second cause of bias is the underreporting of positives [12].

In short, the data collected about COVID-19 so far worldwide has generated limited knowledge. The important indicators that would describe the pandemic in a more accurate manner are still largely absent. Real-world evidence addresses this shortcoming. This approach has been utilized to combat other similar seasonal infections. To assess seasonal influenza, standard indicators have included an estimate of the number of symptomatic illnesses, medical visits, hospitalizations, and deaths per 100,000 and per annum. These indicators are still unknown for SARS-CoV-2. The percentage of hospitalizations and deaths of all infected individuals is significantly harder to estimate due to the availability and reliability of population-wide tests. This knowledge gap forces overreliance on statistical models that are highly unreliable without accurate input data.

What information do we need to collect at the hospital level to answer epidemiological questions?

- Population

The manifestation of SARS-CoV-2 depends, among other factors, on the individual's age, comorbidities and immune status. While in most people the course of infection is mild or entirely asymptomatic, others develop severe disease that requires extensive supportive treatment. We have directed our attention to collecting data on patients whose primary diagnosis at hospitalization is COVID-19 and whose condition requires inpatient treatment.

- Chronology

To provide measurable output for epidemiologists, there is a need to collect data points describing the development of the disease accurately over time. Specifically, epidemiologists need to know the time lag between the onset of symptoms and hospitalization and time to death. When presented chronologically, this information enables the detection of shifts in pathogenicity and virulence of the virus.

The time lag between the onset of symptoms and the time of testing and availability of results indicates how much a timely diagnosis and aggressive treatment improves outcomes.

The time spent in regular hospital care, in intensive care units and on mechanical ventilation and other types of oxygen support enable classification of severity of the disease and efficacy of any therapeutic interventions.

- Type of testing

It is safe to assume that most mild cases remain undiagnosed. How does time from onset of symptoms to diagnosis affect outcomes? The type of test used, COVID-19 RT-PCR, Human SARS-CoV-2 IgG/IgM (2019-nCoV/Coronavirus) ELISA Kit, or assumed diagnosis based on clinical presentation and medical imaging needs to be captured to understand how the type of test and time lag between onset of symptoms, diagnosis and hospitalization affect course of the disease, probability of serious complications and the risk of death.

Treating COVID-19

Hospital care for COVID-19 patients currently consists of infection control and supportive care, such as high flow oxygen and positive pressure ventilation.

There are also a range of approaches tried so far:

- The use of glucocorticoids is limited to the management of COPD based on previous experience with influenza, MERS and SARS.
- The value of NSAIDs is uncertain, although some clinicians believe they may in fact be harmful.
- Drugs and biologics administered to COVID-19 patients include remdesivir, chloroquine, hydroxychloroquine and IL-6 inhibitors, although their efficacy is not yet substantiated.
- Antiretrovirals have been tried as well, with some success reported for favipiravir [13].
- On March 24, 2020, the FDA permitted the emergency use of convalescent plasma in severe and life-threatening COVID-19 cases [14].

The number of new treatments tried is likely to increase.

The important indicators required to understand the epidemic better include the number of hospitalized patients who require intensive care, what type of interventions are required, and for how long. It is imperative to gain insight into treatment effectiveness to rapidly adjust clinical protocols as more data becomes available. At the same time, for the sake of patient safety it is essential to understand the harmful effects of drugs in specific clinical scenarios as early as possible. The systematic collection of real-world evidence can make this happen.

Reducing Burden on Practitioners and Researchers

Reducing burden on practitioners and researchers involves two aspects: use of better data to reduce treatment demands and simple, quick collection of data points. With both achieved, data such as that found below could be applied quickly.

A series of studies published in Lancet evaluated the risk of death in patients with various co-morbidities. Patients with high Sequential Organ Failure Assessment (SOFA) score on admission are more likely to die [15]. Zaim et al. (2020) stressed the risk of progression to multi-organ failure, especially in the presence of comorbidities and organ injury. Patients with significant co-morbidities were more likely to develop complications and die [16].

According to a study performed on 191 patients in Jinyintan Hospital and Wuhan Pulmonary Hospital, older age, high SOFA score on admission, and elevated d-dimer were associated with a higher risk of death [17].

The Center for Disease Control and Prevention (CDC) warns that the severe form of COVID-19 most threatens people who have underlying medical conditions, namely chronic lung disease or asthma, serious heart conditions, severe obesity, diabetes, liver disease, and patients on dialysis or with conditions that compromise the immune system [18].

Optimizing Time of Hospitalization to Improve Outcomes

Would SOFA score on admission be lower had these patients been hospitalized earlier? Would a risk score chart that accounts for symptoms as well as significant comorbidities enable more effective triage and management of patients? Would earlier hospitalization and symptom management prevent escalation of symptoms and progression of COVID-19 and treatment in intensive care units? How much would the outcomes improve had patients at risk been hospitalized earlier? Does earlier hospitalization, as measured by SOFA score on admission, decrease the need for intensive care?

- The most appropriate indicators need to be identified to enable detection of candidates for hospitalization before they deteriorate and their SOFA score progressively worsens.
- Relevant comorbidities need to be known at time of testing to allow triage personnel to prioritize and plan hospital admissions.
- The impact of relevant comorbidities needs to be quantified in terms of prolongation of hospitalization, the need for critical care, and the risk of death.

Charlson Comorbidity Index [19] is an important predictor of risk of death in COVID-19 patients as well as length of time in critical care. Significant comorbidities contribute to all-cause mortality under normal circumstances, and during the coronavirus crisis as well.

Charlson Comorbidity Index (CCI) is a widely used tool that predicts the ten-year survival depending on age and comorbid conditions. Comorbidities used to calculate the score include diabetes mellitus (uncomplicated and with end-organ damage), peripheral vascular disease, COPD, liver disease (mild, moderate and severe, as defined), moderate or severe chronic kidney disease, solid tumors localized and metastatic, congestive heart failure, cerebrovascular accidents or AIDS. In COVID-19 patients, CCI is useful to standardize reporting of significant comorbidities. Past studies observed that additional risk factors for COVID-19 patients include hypertension, obesity and smoking.

SOFA score on admission and Charlson Comorbidity Index seem to be the most appropriate indicators to measure the impact of COVID-19 in the context of a patient's overall health. Most patients with COVID-19 have mild symptoms and stay at home, waiting for the disease to run its course and pass. In some patients however, the symptoms progress and require hospitalization. Earlier detection of symptoms that are likely to progress into severe disease, in combination with the patient's individual risk score would be instrumental for triage personnel. Armed with continuously updated risk score charts, first responders would be in a better position to advise patients to either continue symptomatic treatment at home and monitor specific indicators, or to proceed with hospitalization before it is too late. RWD collection methods will enable quantification of impact of comorbidities on length of hospitalization and the need for intensive care.

Real-World Data Collection Techniques

Real-world evidence enhances understanding and RWD collection techniques can rely on routinely collected indicators without placing additional burden on practitioners. Surveys and questionnaires may be used to collect information from hospitals without the need to perform any additional tests or procedures. The design of a questionnaire should address all the critically important gaps in knowledge while keeping the effort required to fill in such survey to the minimum. An additional requirement is the need to serve multiple monitoring systems and initiatives at the same time. To avoid the need for duplicated collection of overlapping datasets, these critical knowledge gaps can be pooled and combined in a single survey. The final dataset should provide information on epidemiological indicators, efficacy and safety of various management approaches including experimental and off-label treatments and adverse drug events associated with the use of novel treatment protocols and prolonged use of supportive care interventions.

There is currently no dedicated disease registry for COVID-19 patients, so our survey addresses a critical need. The data gathered as part of routine care can be very helpful in determining the most effective therapy protocols and management strategies. Retrospectively capturing U.S. case reports since the beginning of the pandemic would provide insight faster than limiting the survey to patients who are leaving hospitals right now. Limiting the survey geographically to U.S. hospitals will only eliminate some of the methodological differences that make treatment approaches and outcomes so difficult to compare.

Value of Real-World Data, Real-World Evidence in Clinical Care and Research

The FDA is increasingly embracing real-world evidence to monitor post-market safety of drugs, to support regulatory submissions, and to generate data to support clinical decisions. A series of guidelines exist on the nuances of utilizing real-world data to generate evidence [20]. The agency appreciates that real-world data is ideally suited to support large simple trials and pragmatic clinical trials as well as observational studies. Furthermore, real-world data approaches can provide results quickly and in sufficient quantity and quality of evidence.

During the COVID-19 pandemic, it is essential to collect information that fills the current knowledge gaps to reduce uncertainty relating to this novel disease. This data collection effort shall serve more than one purpose and provide insight into the effectiveness of novel therapies, quickly detect harmful interventions, and facilitate triage and timely hospitalization of patients who are most at risk of rapid deterioration.

Differing methodologies produce vastly different results due to the wide range of symptoms and their severity, differences in criteria for diagnosis of COVID-19 on admission and on discharge, differences in recording COVID-19 on death certificates, and the unprecedented response of the media that influence decision-making at both institutional and individual level.

Significant knowledge gaps exist concerning the infectivity and spread of the virus and the risk factors linked to the development of a critical disease. Uncertainties exist regarding time-lapse from the onset of symptoms and the need for hospitalization, duration of symptoms that require hospital care and intensive care management, interventions, and treatments that can reduce the length of hospitalization and need for invasive procedures. These knowledge gaps need to be addressed with greater accuracy and confidence to optimize patient outcomes, reduce the need for intensive care, reduce avoidable patient casualty, and facilitate appropriate distribution of resources within anticipated hotspots.

Our survey was designed to collect information about hospitalized Covid-19 patients at the point of care in a structured and standardized manner and make this cumulative experience available to the public. Data collected this way enables real-time and future exploratory analysis. The data can be further utilized to generate hypotheses on the possible relationships between timelines, risk factors, laboratory markers, interventions and outcomes, and direct future research to specific focus areas. The aggregated dataset will be made available to other researchers and physicians in the form of interactive dashboards.

More focused data collection efforts within formal clinical trials will always be necessary to prove or disprove efficacy and safety of a specific intervention. However, a broad, general, non-discriminatory approach to collecting data directly at point of care that standardizes the input utilizing widely used, clinically relevant thresholds, is a good way to quickly gain insight into multiple problem areas at once. Systematic data collection effort that enables instant visibility of results through interactive analytical dashboards will reduce time to insight and help guide future research.

To Summarize

In the throes of a global pandemic, uniform collection and analysis of such data is imperative. Collecting relevant information such as treatment outcomes and adverse drug

events at the point of care will help the medical and scientific communities evaluate the data in near-real-time and respond accordingly by adjusting treatment protocols and triage practices. Every new patient should have better odds of survival and full recovery as the system learns from past experiences.

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