

The Value of Medical Registries and Observational Studies Early in Pandemics: The COVID-19 Experience

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Summary

- Observational studies and registries played key roles in rapid understanding of the novel SARS-CoV-2 during the COVID-pandemic.
- Advancements in the use of registries is necessary to prepare better for future public health emergencies.

Abstract:

Whereas randomized clinical trials remain the gold standard for evaluating new therapies for infections, we argue that registries and observational studies early in the Covid-19 pandemic provided invaluable understanding of the natural history and preliminary data on risk factors and possible treatments. We review the data from the current pandemic, the history of registries in general and their value in public health emergencies. Lessons from these experiences should be incorporated into rigorous planning for the next pandemic.

Keywords: COVID-19; Pandemics; registry; medical registries; observational studies

Accepted Manuscript

*** Introduction**

On March 11th 2020, The World Health Organization (WHO) declared “COronaVirus Disease 2019” (COVID-19) a pandemic. Globally as of 20 March 2021, there have been 121 969 223 confirmed cases and 2 694 094 deaths reported to WHO.¹ The cause, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the *Coronaviridae* family of enveloped, positive-sense, single-stranded RNA viruses that infect a broad range of vertebrates. Due to sequence similarities with RaTG13 bat and pangolin coronavirus strains, it is currently thought that SARS-CoV-2 has a zoonotic origin and subsequently acquired human-to-human transmission ability.² SARS-CoV-2 infection is associated with a fatality rate of 1–3%.³

The COVID-19 pandemic has impacted all aspects of society, and efforts to control the virus have required infectious disease physicians to learn about its many facets as quickly as possible. Registries have played a critical role. In this review, we describe the many COVID-19 registries and observational studies, discuss their history, method of development of registries, their early role in understanding the COVID-19 pandemic, and highlight their importance for responses to future public health threats.

*** Data from early COVID-19 studies**

When the COVID-19 pandemic hit, the only certainty was how little was known about the illness and causative virus. Various scientific efforts were initiated, and investigators launched clinical trials and cohort studies to evaluate therapeutics and address their impact on the novel coronavirus. The creation of registries of patients with COVID-19 was initiated globally. Data from large observational studies and registries of COVID-19 patients quickly led to important discoveries and rapid knowledge: analysis of the genetic susceptibility in patients with severe COVID-19,⁴ evaluating the safety and efficacy of hydroxychloroquine^{5,6} and dexamethasone⁷, studying the association between the use of angiotensin-receptor

blockers and angiotensin-converting enzyme inhibitors and the risk of COVID-19,⁸ investigating COVID-19–related diabetes,⁹ and assessing and predicting outcomes in hospitalized patients with COVID-19.^{10–13} Retrospective observational cohort studies in hospitalized patients from Wuhan, China, and then similarly from cohort studies in the U.S., Italy, Singapore, and other countries offered valuable early information on natural history. Importantly, registries contributed to our understanding of asymptomatic transmission of COVID-19. The COVID-19 living evidence database¹⁴ is a living systematic review system that saves high quality online summaries of health research, updated as new research becomes available, and enabled by improved production efficiency and adherence to the norms of scholarly communication (Elliott et al, PLoS, 2014).¹⁵ This database has been the basis for many systematic reviews and meta-analyses addressing the transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections.¹⁶ Early on, investigators understood that between 17% and 20% of people with COVID-19 infections were asymptomatic,^{16,17} and 49% of people initially defined as asymptomatic went on to develop symptoms.^{18,19} However, case reports and outbreaks highlighted the role of asymptomatic transmission. Overall, while registries are important, they can only reflect what clinicians see, and during a pandemic it follows that there is a bias towards more severe cases.

**** Global COVID-19 registries and observational studies***

It was critical to analyze a high volume of reliable patient-level, accurately attributed, nationally representative data. This is where the registries became valuable and highly essential. Specifically, there have been global efforts to create data registries for rapidly understanding the interaction of COVID-19 in patients with a number of underlying diseases: the large registries of COVID-19 in patients with cancer, such as CCC19 (the COVID-19 and Cancer Consortium),²⁰ UKCCMP (the UK Coronavirus Cancer Monitoring Project)²¹ and TERA-VOLT (Thoracic Cancers International COVID-19 Collaboration)²². These registries

helped characterize the outcomes of patients with cancer and COVID-19 and identify potential prognostic factors for mortality and severe illness. Another example is the global registry of patients with COVID-19–related diabetes (covid diab.e-dendrite.com) established by an international experts participating in the CoviDIAB Project.⁹ The goal of this registry was to establish the extent and phenotype of new-onset diabetes in COVID-19, assess the impact of the metabolic syndrome on severity of COVID-19, investigate the epidemiologic features and pathogenesis of COVID-19–related diabetes and gain clues regarding appropriate care for patients during and after the course of COVID-19.⁹ The international rheumatology community created the COVID-19 Global Rheumatology Alliance²³ to generate rapid data to inform the care of individuals with rheumatic disease and those using immunomodulating therapies. Information from this database continues to provide timely and responsive real-world data where large literature gaps exist, informing providers of treatment patterns for individuals diagnosed with COVID-19, and offering a better understanding of possible risk factors associated with severe outcomes in the rheumatic disease population.²³ The largest cohort to date of patients with chronic liver disease affected by SARS-CoV-2 infection was collected through two collaborative, large-scale international reporting registries (SECURE-cirrhosis coordinated by University of North Carolina, Chapel Hill, USA and COVID-Hep.net coordinated by University of Oxford and supported by The European Association for the Study of the Liver).²⁴ Other examples of international registries are the PRIORITY Study (pregnant women with COVID-19, UCSF), the International Dermatology COVID-19 Registry (dermatologic manifestations), and the Extracorporeal Life Support Organization (ECMO patient registry). Large registries involving COVID-19 in various patient populations have been used in different fields of study, including cardiovascular health^{26–28}, critical care^{29–31}, surgery^{32–35}, transplantation³⁶, radiology³⁷, dermatology^{38,39}, and pediatrics⁴⁰. One of the largest nationwide registry initiatives in the United States is the National COVID

Cohort Collaborative (N3C) (covid.cd2h.org) aggregates and harmonizes electronic health record data across clinical organizations, and is a novel partnership that includes the Clinical and Translational Science Awards Program hubs, the National Center for Advancing Translational Science, the Center for Data to Health and the community.⁴¹ The N3C registry will be a resource for the next 5 years to understand long-term health impact of COVID-19 and enable novel analyses to address COVID-19 as well as to demonstrate that this collaborative analytics approach could be invaluable for addressing other diseases in the future.

At our institution in June 2020, we established a COVID-19 registry (officially called the VCU Registry of SARS-CoV-2(VCU-RS)),⁴² composed of a biobank of blood samples from COVID-19 patients linked to a database that stores a wide array of information about those patients. The data set the stage for long-term investigations through this institutional resource to allow translational scientists to engage in research studies around COVID-19 to answer current and future scientific questions.

**** Definition of Registries***

Registries are considered an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individuals who have either a particular disease or a risk factor(s) known or suspected to cause adverse health effects, to be useful for specific public health purposes.^{44,45} A registry records data about the health status of patients and the health care they receive over time (National Quality Registry Network (NQRN), n.d.).⁴⁶

**** History of registries***

To our knowledge, the National Leprosy Registry of Norway, which was established in 1856 by Ove Guldberg Høegh (1814–63), the first Chief Medical Officer for Leprosy in Norway, was probably the first patient registry created.⁴⁷ G.H. Armauer Hansen (1841–1912), the world renowned Norwegian who in 1873 discovered the leprosy bacillus, used data from this

registry for his epidemiological, groundbreaking research in Leprosy. The publications and analyses based on the Leprosy Registry provided the foundation for public health policies (particularly isolation and quarantine policies); therefore the Leprosy Registry was the main reason why Leprosy eventually disappeared from Norway.⁴⁷ In the United States, the first established patient registry was the Codman bone sarcoma registry founded in 1920. In 1935, the first state centralized data cancer registry was built in Connecticut. Then in 1973, the first national cancer registry, ‘Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute’, was established. By 1993, most states had passed laws requiring cancer registries. The earliest known reference of a healthcare delivery organization using a formal disease registry strategy to improve care was at GroupHealth of Puget Sound in the early 1980s for diseases other than cancer, known as “clinically related information system”. Registry use was primarily for retrospective clinical research and local quality improvement purposes. Prospective registries developed slowly. The Framingham Heart Study, in operation since 1948, is a notable example of a registry initiative that, through its extensiveness and comprehensiveness, continually provides the medical community an outstanding source of information on trends associated with treatment for cardiovascular and other conditions.⁴⁸ The National Registry of Myocardial Infarction, an industry-sponsored initiative, has, since 1990, been the foundation underlying many important treatment guidelines for the management of heart attacks.⁴⁹

Since the early 2000s, there had been an increase in the number of chronic diseases registries such as the New York City’s HbA1C Registry (NYCAR) to help health providers keep track of patients with diabetes.⁵⁰ Another example of disease registry is the New York State CABG Registry that tracks all cardiac bypass surgery performed in the state.⁵¹ In the field of infectious diseases, registries have proven extremely useful, such as in the study of Tuberculosis.^{52–54} Registries were paramount in understanding the global epidemiology and

disease burden of Tuberculosis, and the global Tuberculosis report submitted to the WHO in 2012 was generated using registry-based data.⁵⁵ During the 2009 influenza A (H1N1) pandemic, registries played a vital role in advancing the knowledge about the disease and planning for influenza seasons thereafter.⁵⁶ Registries are used in several domains that include patient care, public health, service and technology, and research.^{44,57} Examples of clinical registries are those that focus on a disease (e.g., cystic fibrosis), a procedure (e.g., coronary artery bypass grafting surgery) or the performance of a device (e.g. artificial joint).^{46,58} Linkage of registry data with other databases like biorepositories and the use of data in clinical trials will advance public health studies in numerous fields. Today, registries are the basis for most scientific efforts and research studies and are shaping public health and pushing boundaries with its unparalleled ability to influence policies and lawmakers.

****Strengths and limitations of registries***

Registries are useful but are limited by unknown ascertainment among a population or unknown denominator, so they cannot be representative of cases among a population. Patient data derived from a cohort of all hospitalized patients with laboratory-confirmed COVID-19 population-based surveillance data are more informative. Observational studies and registries have accelerated the development of research studies and resulted in fast-tracking publications. However, they have advantages and drawbacks. For instance, observational studies supported the initial interest in hydroxychloroquine, but the only way to definitely assess its clinical benefit was through implementing randomized controlled trials (RCTs). Such data showed the initial observational studies were misleading;²⁵ even though some observational studies did show benefit. What has looked promising from results of in vitro and in observational studies did not pan out in RCTs. In contrast with registries, despite their advantages, RCTs are not fully representative of selected patient populations; due to their restrictive inclusion and exclusion criteria. Registries are generally less expensive and deliver

results more quickly than RCTs, can have very large sample sizes, assess a broad range of outcomes and provide information on treatments in patient groups that are usually excluded from RCTs.⁴³ A critical point is that registries complement RCT by providing information about populations not studied in RCT. Though not generalizable to all populations, such registries are used to understand causal relationships about some populations.

The existence of registries led to advancing our understanding of COVID-19 relatively quickly. Further, registries may play an important role in understanding the long term COVID-19 symptoms and outcomes, and in evaluating vaccines effectiveness over time. Registries are likely to continue to play a vital role in later phases of the pandemic.

*** *Developing a registry***

Developing a registry is accomplished by multi-stakeholder collaborations, working together to perform tasks to meet the purpose of the registry.⁴⁶ Data collection is generally purpose driven (i.e. not dependent on or limited to previously available or existing data). The process of creating a registry involves capturing data elements under predefined protocols, accessing multiple data sources, securely managing data and collecting the highest possible number of cases from a defined population to make it a representative data source, augmented by explicit efforts to perform quality checks and maintain systematic constant data update.^{44,57}

According to Gliklich and colleagues^{59,60}, when planning a registry, it is desirable to follow these initial steps: (1) articulate the purpose of the registry; (2) determine if a registry is an appropriate means to achieve the purpose; (3) identify key stakeholders; and (4) assess the feasibility of a registry. Once a decision is made to proceed, the next considerations in planning are to (5) build a registry team; (6) establish a governance and oversight plan; (7) define the scope and rigor needed; (8) define the data set, patient outcomes, and target population; (9) develop a study plan or protocol; and (10) develop a project plan. Registry

planners should also recognize the importance of periodic critical evaluations of the registry by key stakeholders to ensure that the objectives are being met (Gliklich, 2014, p. 29).^{59,60}

*** *Registries in public health emergencies***

There is a myriad of questions that arise during public health emergencies, and registries serve as a critical infrastructure and valuable starting point for key insights. Moreover, registries have inherent flexibility as needs evolve during pandemics. The Global Initiative on Sharing Avian Influenza Data (GISAID) EpiCov database⁶¹ is a registry of novel coronavirus mutations and potential variants that enables rapid and open access to COVID-19 virus data. This initiative increases the likelihood that emerging variants are identified and can be assessed in a timely fashion.⁶¹ The GISAID EpiCov database was behind the rapid discovery of new SARS-CoV-2 variants in some countries. The reported cases affected by new variants in the United Kingdom, Denmark, the Netherlands, Australia, Belgium and South Africa were identified through the GISAID EpiCov database.⁶² The Global Evaluation of SARS-CoV-2/hCoV-19 Sequences (GESS) (<https://wan-bioinfo.shinyapps.io/GESS/>) is another database of viral genome sequences based on the analysis of single nucleotide variants from high-coverage and high-quality hCoV-19 viral genomes downloaded from GISAID as of July 2020 and updated weekly.⁶³

When executed properly, registries can pivot successfully and adjust to emerging priorities and questions. In addition, they can be leveraged by a biorepository nexus to support pathobiology research. Registries are one of the best methods to leverage real-world data during pandemics. With most registries designed for specific disease conditions, they carry important personal health information that allows the assessment of natural history, epidemiology and outcomes of the disease and thus can help improve health care quality even in absence of a cure for the disease. The readiness of data in registries, especially in

electronic database systems, facilitates the identification of patients that qualify for certain clinical trials, the analysis of interventions and the evaluation of treatment options.

Registries facilitate international collaborations for the purpose of the legal sharing of data for health advancements.⁶⁰ They can also provide a huge pool of information instantly, allowing rapid decision making and conclusions in the relevant area of focus since many registries have wide scopes of data collection. Registries are often handled by professionals in every domain from collection to management, which can be combined with the reliability of electronic systems to ensure data safety and accuracy, minimizing human error. With computerized registries, processing and analyses are faster and more accessible. Furthermore, registries are constantly evolving and thus have the potential for next generation technological advancements. It is clear that information on COVID-19 is fragmentary at best with the pandemic's massive numbers of patients challenging the health systems. There is an urgent need for epidemiological studies to further our understanding of the health impact of COVID-19. Disparate specialty groups around the globe have issued urgent requests and appeals to their societies to develop national or regional COVID-19 databanks. As part of building a public health robustness to respond to the next pandemic, we suggest developing registries that can pivot quickly to new challenges and be activated on short notice to gain early knowledge of the new issues. It is necessary to enhance the processes of establishing high quality registries in short periods of time and improve electronic data capture and storage. Knowing the advantages that registries offer, it is important to remember that they have their own limitations as well, similar to those for observational studies. An early signal for the value of a therapy may later be shown to have been misleading. We have shown nevertheless their value in preparing for the next pandemic.

Notes:

Funding: No funding support for this manuscript.

Potential conflicts: The authors have no conflicts of interest.

Accepted Manuscript

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