JH-CROWN COVID-19 PMAP Registry

Description

- Based on Precision Medicine Analytics Platform (PMAP)
- Data access approved by COVID-19 Data Research Evaluation (CADRE) committee
- Includes: Patients (all ages) seen at any Johns Hopkins Medical Institution facility (both inpatient and outpatient, in-person or via video consult or lab order) since 1/1/2020 documented in Epic as having confirmed COVID-19 or suspected of having COVID-19.
  The cohort is defined as follows:
  - Having a completed laboratory test for COVID-19 (whether positive or negative)
    Or
  - Having and ICD-10 diagnosis of COVID-19 (either recorded at the time of the encounter, entered on the problem list, entered as medical history, or appearing as a billing diagnosis)
    Or
  - Flagged as a "patient under investigation" for suspected or confirmed COVID-19 infection (Infection flag)
- N=1049 admissions as of 5/4/2020
- Population description
  - Largely from Baltimore-Washington Corridor
    - Within Baltimore City, concentrated on the East side
  - 40% Black, 34% White
  - Median age = 63 (IQR 49-75)
  - Median Charlson Comorbidity Index = 1 (IQR 0-3)
  - ~50% are referral/transfer patients (including external and internal referral/transfers)
- Data elements – see data dictionary

REGISTRIES

Strengths: Real-life observed data; objective measurements; follow-up over time; with appropriate statistics, can assess multiple exposures and multiple outcomes; and can at times inform causal hypotheses.

Potential Biases/issues - associated generally with registries

Internal validity: The degree to which measured associations reflect true associations in the study population.

- Information bias: Data are collected for clinical vs. research purposes and may contain errors or missing values. [1–5]
  - Measurement error: Incorrect assignment of exposure or outcome status. May come into play in particular with patient-reported exposures (e.g. smoking). Most problematic when measurement error is differential (i.e. routinely under- or over-reported) by exposure or outcome status.
  - Missing data: Missing values in exposure, outcome, or covariates. Most problematic when data points are missing systematically and cannot be imputed using observed characteristics (i.e. "missing not at random")
  - *Potential information biases associated specifically with the CROWN registry*
    - Left-censoring: As a tertiary care center, a large portion of our Covid19 admissions are referrals who are further along in their disease course. Earlier clinical events will have already occurred for a non-trivial subset of them. For example, in a study of the need for oxygen support, nearly half of the Crown cohort arrived on oxygen. The date of initiation is therefore left censored. The people in our cohort do not represent the population disease trajectory (Zeger). Within transfers there are also subgroups of those transferred external to JHHS and those transferred within JHHS (i.e. Sibley to JHH).
    - Left-censoring-measurement bias: There are differences in the measurements (availability, type, etc.) between referral/transfer vs. non-referral/transfer patients.

        - Outcome dependent sampling: The probability of observing the primary exposure variables depends on the observed value of the outcome variable.
        - Misclassification of outcomes: If discharged cases die from COVID-related symptoms outside of JHM, they may be misclassified as recovered vs. deceased. CRISP could be used to obtain f/up data of discharged cases for a period of time.
- Confounding: Bias of the exposure-outcome association due to baseline differences among the exposure groups in risk factors for the outcomes.[6]
    - Confounding by indication: A specific type of confounding where treatments are selected based on a clinical indication (e.g. disease severity) which also affects the outcome.[4,7]
        - There is a subgroup of patients (clustered within specific hospital sites) that have a pre-existing DNR/DNI/Comfort care (due to baseline characteristics such as dementia and/or poor functional status) for whom the course of clinical treatment (and related outcomes) will be different than those w/o a DNR. Example, at Suburban, 76% of patients who died were never ventilated and were largely if not all DNR/DNI/Comfort care patients. By comparison at JHH, 16% of patients who died were never ventilated (16%) (Thiemann).
        - There will be a subset of patients that evolve to have a DNR which is likely due to disease severity and this will affect their course of clinical treatment and outcomes.
- Threats to internal validity in survival or time-to-event analyses
    - Nonignorable right censoring: A final disposition code (e.g. death or discharge) is unavailable and this censoring is related to exposure or outcome status.[9,10] Even with multiple months of follow-up, currently 28% of the Crown cohort is still hospitalized pending outcome. Reports about the completed cases (discharged or deceased) are biased because the pending cases are not like the rest; they tend to be sicker so a larger fraction will die. This is an example of non-ignorable right censoring that must also be accounted for, even in reporting basic rates (Zeger).
    - Competing risks: Another, mutually exclusive outcome can occur before your outcome of interest occurs (e.g. death before being put on a ventilator).[8]
    - Survivorship bias: Individuals must live long enough to be "exposed" to a treatment. For example, patients who die shortly after testing positive may be over-represented in the "control" group for a particular treatment, giving the treatment group an artificial survival advantage.[11,12]

<u>External validity / selection bias</u>: because of the way patients enter the registry, exposure-outcome relationships may differ systematically between the registry population and the target populations researchers wish to generalize to.

- By including only care-seekers, clinical registries often systematically under-capture: 1) Mild or asymptomatic cases, 2) Uninsured people or other patients with barriers to accessing care, and 3) People who die at home.[12]
- Berkson's bias: A type of selection bias that is particular to clinic-based case-control studies.[2] If exposure and outcome both cause a person to present to clinic, when we "condition on" clinic through recruitment, we can see spurious associations between exposure and outcome. To mitigate the risk of Berkson's bias, investigators might wish to select matched, population-based controls

References

1. VanderWeele TJ, Hernán MA. Results on differential and dependent measurement error of the exposure and the outcome using signed directed acyclic graphs. *Am J Epidemiol*. 2012. doi:10.1093/aje/kwr458
2. Westreich D. Berksons bias, selection bias, and missing data. *Epidemiology*. 2012. doi:10.1097/EDE.0b013e31823b6296
3. Lambert J. Statistics in brief: How to assess bias in clinical studies? *Clin Orthop Relat Res*. 2011. doi:10.1007/s11999-010-1538-7
4. Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health*. 2004. doi:10.1136/jech.2003.008466

5. Psoter KJ, Rosenfeld M. Opportunities and pitfalls of registry data for clinical research. *Paediatr Respir Rev*. 2013. doi:10.1016/j.prrv.2013.04.004
6. Porta M. A Dictionary of Epidemiology-Oxford University Press. 5th Ed.
7. Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from real world data: Propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ*. 2013. doi:10.1136/bmj.f6409
8. Noordzij M, Leffondré K, Van Stralen KJ, Zoccali C, Dekker FW, Jager KJ. When do we need competing risks methods for survival analysis in nephrology? *Nephrol Dial Transplant*. 2013. doi:10.1093/ndt/gft355
9. Shih WJ. Problems in dealing with missing data and informative censoring in clinical trials. *Curr Control Trials Cardiovasc Med*. 2002. doi:10.1186/1468-6708-3-4
10. Ranganathan P, Pramesh C. Censoring in survival analysis: Potential for bias. *Perspect Clin Res*. 2012. doi:10.4103/2229-3485.92307
11. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: A comparison of methods. *Am J Epidemiol*. 2005. doi:10.1093/aje/kwi307
12. Lipsitch M, Donnelly CA, Fraser C, et al. Potential biases in estimating absolute and relative case-fatality risks during outbreaks. *PLoS Negl Trop Dis*. 2015. doi:10.1371/journal.pntd.0003846