The Daily COVID-19 Literature Surveillance Summary

October 08, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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EXECUTIVE SUMMARY

Understanding the Pathology

- Physicians from Pisa University Hospital (Italy) remark on Zhao et al's (2020) findings on ABO Blood Group Correlations With COVID-19, stating that their observed association between blood group A and increased risk of COVID-19 may be due to their choice in cohort. In the authors' own study of a group of 7,713 healthy blood donors, there was no significant difference in rate of anti-SARS-CoV-2 nucleocapsid IgG based on blood type and there are other studies with similar findings. While this study does not eliminate the need to examine differential rates of infection and outcomes for COVID-19 patients based on blood type, it does indicate that previous study results may be biased by group selection.

Transmission & Prevention

- Vaccines that present the α-gal epitope produced by glycoengineered bacteria or yeast had increased uptake by antigen presenting cells (APCs) by 10 to 200 fold when given to mice. Since anti-Gal is a natural immunoglobulin G (IgG) in the human serum, authors state that vaccines with the α-gal epitope may increase anti-viral immune response of T cells against the SARS-CoV-2 virus. Authors suggest development of vaccines with α-gal epitopes have been shown to be safe for use in humans through clinical trials and could offer improved efficacy via maximized immune response to SARS-CoV-2.

Resources

- A data-driven, ontology-based, and natural language processing approach for analyzing COVID-19 clinical trials was developed by a high school student from The Harker School in San Jose, California who data mined ClinicalTrials.gov using Application Programming Interfaces (APIs) to compile relevant data from COVID-19 clinical trials including drug treatments and interventions, outcomes, Medical Subject Heading (MeSH), and Human Phenotype Ontologies (HPO). The results (available at http://covidresearchtrials.com) provide a public compilation of unique reports in each category analyzed, which could offer guidance to the global research community to support development of future clinical trials, treatments and interventions, and meta-analyses, as well as general insight into the response to COVID-19.

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EPIDEMIOLOGY

CORONAVIRUS 2019 (COVID-19) INFECTIONS AMONG HEALTHCARE WORKERS, LOS ANGELES COUNTY, FEBRUARY - MAY 2020

Hartmann S, Rubin Z, Sato H, OYong K, Terashita D, Balter S.. Clin Infect Dis. 2020 Aug 17:ciaa1200. doi: 10.1093/cid/ciaa1200. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

The Los Angeles County Department of Public Health (LAC DPH) conducted an observational study analyzing data from interviews with healthcare workers (HCWs; n=5118) who were infected with COVID-19 from February 2020 to May 2020 (Figure 1). Based on the findings of this study (see summary) authors emphasize the importance of conducting and analyzing interviews with infected HCWs to better understand the burden of COVID-19 among HCWs and tailor the public health response.

SUMMARY

Specific findings from this study include:
- Hospitalization and mortality rates due to COVID-19 among HCWs were 5.3% and 0.7%, respectively.
- Rates of HCW infections were higher among nurses and within long-term facilities.
- 44% of HCWs reported having "healthcare exposures within their facility" when asked if they had a "known exposure to COVID-19" (Table 3).
- 64.2% of HCWs reported having worked during their infectious period (Table 4).

ABSTRACT

Across the world, healthcare workers (HCW) are at a greater risk of infection by the novel coronavirus 2019 (COVID-19) due to the nature of their work. The Los Angeles County Department of Public Health (LAC DPH) set out to understand the impact of COVID-19 on healthcare facilities and HCWs by tracking and analyzing data from case-patient interviews of HCWs. As of May 31st, over three months into the pandemic, nearly 5,500 positive HCWs were reported to LAC DPH, representing 9.6% of all cases. Cases reported working in 27 different setting types, including outpatient medical offices, correctional facilities, emergency medical services, etc., with the highest proportion from long-term care facilities (46.6%) and hospitals (27.7%). Case-patients included both clinical and non-clinical roles, with nearly half (49.4%) of positive HCWs being nurses. Over two-thirds of HCWs (68.6%) worked at some point during their infectious period and nearly half (47.9%) reported a known exposure to a positive patient and/or co-worker within their facility. Overall, compared to all LAC cases, HCWs reported lower rates of hospitalization (5.3% vs. 12.2%) and death (0.7% vs. 4.3%) from COVID-19. There are many factors that increase HCWs risk of infection, including high risk work environment, limited supply of personal protective equipment, and even pressure to help and work during a pandemic. In response to these data, LAC DPH created resources and provided guidance for healthcare facilities to best protect their patients and staff during the COVID-19 pandemic.

FIGURES

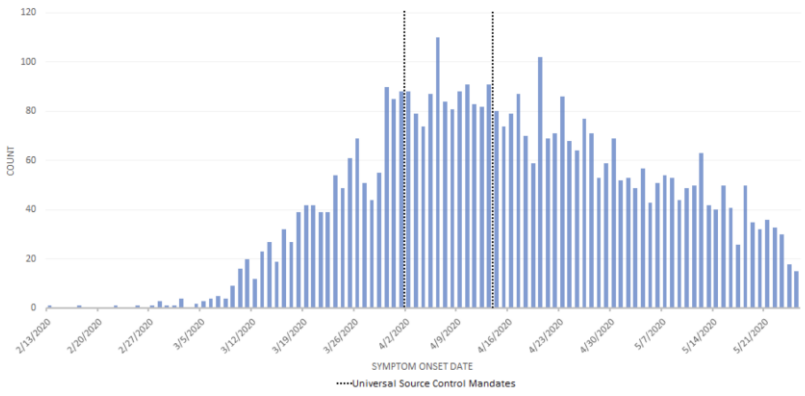

Figure 1. Reported Date of Symptom Onset for COVID-19 Positive Healthcare Workers, Los Angeles County, through May 31, 2020.

Healthcare Exposure	Count	Percent
Positive Patient	396	7.7%
Positive Healthcare Worker	167	3.3%
Both: Healthcare Worker and Patient	106	2.1%
Healthcare Not Specified	1562	30.5%
Non-Healthcare Exposure		
Household/Family Contact	321	6.3%
Travel	56	1.1%
Social/Community Contact	27	0.5%
Non-Healthcare Not Specified	172	3.4%
Unknown Exposure		
Reported Unknown Exposure	1850	36.1%
Did Not Answer Question	461	9.0%

Table 3. Reported Exposure of COVID-19 Positive Healthcare Workers, Los Angeles County, through May 31, 2020

Worked During Infectious Period	Count	Percent
Day of symptom onset	1241	24.2%
After symptom onset	1146	22.4%
1 - 2 days before symptoms	902	17.6%
Did Not Work During Infectious Period		
More than 2 days before symptoms	631	12.3%
Asymptomatic	313	6.1%
Unknown	885	17.3%

Table 4. Reported Work History of COVID-19 Positive Healthcare Workers, Los Angeles County, through May 31, 2020

PEDIATRICS

IS VITAMIN D DEFICIENCY A RISK FACTOR FOR COVID 19 IN CHILDREN?

Yılmaz K, Şen V.. Pediatr Pulmonol. 2020 Oct 5. doi: 10.1002/ppul.25106. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A case control study of 85 children ages 1 month - 18 years conducted by pediatricians affiliated with Dicle University School of Medicine (Turkey) from March 2020 - May 2020 found significantly lower levels of Vitamin D in children with COVID-19 (n=40; mean 13.14 ug/L, p less than 0.001) compared to matched, control children (n=45, mean 34.81 ug/L), suggesting vitamin D deficiency may be a risk factor for COVID-19 in pediatric patients.

ABSTRACT

OBJECTIVE: COVID 19 is a global health problem that can result in serious complications. The aim of this study was to investigate the prevalence and clinical importance of vitamin D deficiency in children with COVID-19. MATERIAL AND METHODS: This study includes 40 patients who were diagnosed to have COVID- 19 and hospitalized with the real-time reverse transcription polymerase chain reaction (RT-PCR) method, 45 healthy matched control subjects with normal vitamin D levels. The age of admission, clinical and laboratory data, and 25-hydroxycholecalciferol (25-OHD) levels were recorded. Those with vitamin D levels which are below 20 ng/ml were determined as Group 1 and those with >=20 ng/ml as Group 2. RESULTS: Patients with COVID- 19 had significantly lower vitamin D levels 13.14 mug/L (4.19-69.28) than did the controls 34.81(3.8-77.42) mug/L ($p < 0.001$). Patients with COVID- 19 also had significantly lower serum phosphorus (4.09+-0.73 vs. 5.06+-0.93vs (U/L) ($p<0.001$) values compared with the controls. The symptom of fever was significantly higher in COVID- 19 patients who had deficient and insufficient vitamin D levels than in patients who had sufficient vitamin D levels ($p=0.038$). There was a negative correlation found between fever symptom and vitamin D level ($r=-0.358$, $p = 0.023$). CONCLUSION: This is the first to evaluate vitamin D levels and its relationship with clinical findings in pediatric patients with COVID-19. Our results suggest that vitamin D values may be associated with the occurrence and management of the COVID-19 disease by modulating the immunological mechanism to the virus in the pediatric population.

ABO BLOOD GROUP CORRELATIONS WITH COVID-19: COHORT CHOICE MAKES A DIFFERENCE

Focosi D, Iorio MC, Lanza M.. Clin Infect Dis. 2020 Sep 30:ciaa1495. doi: 10.1093/cid/ciaa1495. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Physicians from Pisa University Hospital (Italy) remark on Zhao et al's (2020) findings, stating that their observed association between blood group A and increased risk of COVID-19 may be due to their choice in cohort. In the authors' own study of a group of 7,713 healthy blood donors, there was no significant difference in rate of anti-SARS-CoV-2 nucleocapsid IgG based on blood type (Table 1), and there are other studies with similar findings. While this study does not eliminate the need to examine differential rates of infection and outcomes for COVID-19 patients based on blood type, it does indicate that previous study results may be biased by group selection.

FIGURES

	O	A	B	AB
overall	3499	2299	773	250
IgG+	41 (1.17%)	27 (1.17%)	7 (0.9%)	1 (0.4%)

Table 1. Relative frequency of SARS-CoV2 seropositivity according to blood group in 7713 Italian blood donors

AMPLIFYING IMMUNOGENICITY OF PROSPECTIVE COVID-19 VACCINES BY GLYCOENGINEERING THE CORONAVIRUS GLYCAN-SHIELD TO PRESENT A-GAL EPITOPES

Galili U.. Vaccine. 2020 Sep 29;38(42):6487-6499. doi: 10.1016/j.vaccine.2020.08.032. Epub 2020 Aug 19.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

This review by an immunologist from Rush Medical School in Chicago, Illinois found vaccines that present the α-gal epitope produced by glycoengineered bacteria or yeast had increased uptake by antigen presenting cells (APCs) by 10 to 200 fold when given to mice. Since anti-Gal is a natural immunoglobulin G (IgG) in the human serum, authors state that vaccines with the α-gal epitope may increase anti-viral immune response of T cells against the SARS-CoV-2 virus (Figures 3,4). Authors suggest development of vaccines with α-gal epitopes have been shown to be safe for use in humans through clinical trials and could offer improved efficacy via maximized immune response to SARS-CoV-2.

ABSTRACT

The many carbohydrate chains on Covid-19 coronavirus SARS-CoV-2 and its S-protein form a glycan-shield that masks antigenic peptides and decreases uptake of inactivated virus or S-protein vaccines by APC. Studies on inactivated influenza virus and recombinant gp120 of HIV vaccines indicate that glycoengineering of glycan-shields to present alpha-gal epitopes (Galalpha1-3Galbeta1-4GlcNAc-R) enables harnessing of the natural anti-Gal antibody for amplifying vaccine efficacy, as evaluated in mice producing anti-Gal. The alpha-gal epitope is the ligand for the natural anti-Gal antibody which constitutes ~1% of immunoglobulins in humans. Upon administration of vaccines presenting alpha-gal epitopes, anti-Gal binds to these epitopes at the vaccination site and forms immune complexes with the vaccines. These immune complexes are targeted for extensive uptake by APC as a result of binding of the Fc portion of immunocomplexed anti-Gal to Fc receptors on APC. This anti-Gal mediated effective uptake of vaccines by APC results in 10-200-fold higher anti-viral immune response and in 8-fold higher survival rate following challenge with a lethal dose of live influenza virus, than same vaccines lacking alpha-gal epitopes. It is suggested that glycoengineering of carbohydrate chains on the glycan-shield of inactivated SARS-CoV-2 or on S-protein vaccines, for presenting alpha-gal epitopes, will have similar amplifying effects on vaccine efficacy. alpha-Gal epitope synthesis on coronavirus vaccines can be achieved with recombinant alpha1,3galactosyltransferase, replication of the virus in cells with high alpha1,3galactosyltransferase activity as a result of stable transfection of cells with several copies of the alpha1,3galactosyltransferase gene (GGTA1), or by transduction of host cells with replication defective adenovirus containing this gene. In addition, recombinant S-protein presenting multiple alpha-gal epitopes on the glycan-shield may be produced in glycoengineered yeast or bacteria expression systems containing the corresponding glycosyltransferases. Prospective Covid-19 vaccines presenting alpha-gal epitopes may provide better protection than vaccines lacking this epitope because of increased uptake by APC.

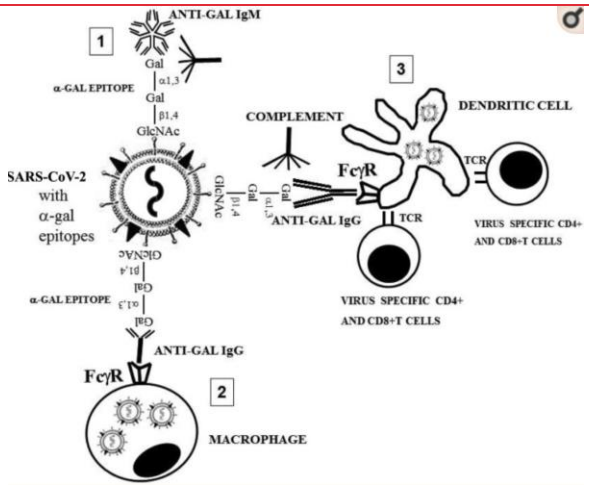

Figure 3. Suggested mechanism for amplification of SARS-CoV-2αgal vaccine immunogenicity by anti-Gal mediated targeting to APC. Inactivated SARS-CoV-2 presenting α-gal epitopes (SARS-CoV-2αgal) is used as a vaccine example. Step 1- Anti-Gal IgM and IgG bind to α-gal epitopes on the vaccinating virus at the vaccination site, activate the complement system which generates complement cleavage chemotactic peptides that recruit APC such as dendritic cells and macrophages. Step 2- Anti-Gal IgG coating the virus targets it for active extensive uptake by the recruited dendritic cells and macrophages, via Fc/Fcγ receptors (FcγR) interaction. Step 3- These APC transport the internalized virus vaccine to the regional lymph nodes and process the virus antigens. Within the lymph nodes, the APC present the immunogenic virus peptides on class I and class II MHC molecules for the activation of SARS-CoV-2 specific CD8 + and CD4 + T cells, respectively. TCR- T cell receptor.

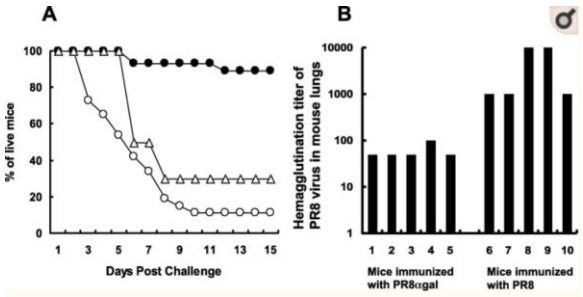

Figure 4. Protection against intranasal infection by a lethal dose of PR8 influenza virus in mice immunized with inactivated PR8 or PR8αgal virus. A. Survival of mice immunized twice with 1 μg inactivated PR8 vaccine (○) in GT-KO mice; PR8αgal (●) vaccine in GT-KO mice; or with PR8αgal (△) vaccine in wild-type mice. The mice were challenged with 2000 PFU of live PR8 in 50 μl (n = 25 per group). Survival data are presented as % of live mice at various days following the challenge. Survival results on Day 30 were similar to those on Day 15 post challenge. B. PR8 virus titers in lungs of GT-KO mice, 3 days after challenge with live virus. The virus titers were assayed in supernatants of lung homogenates from the immunized mice, by hemagglutination of chicken red blood cells (n = 5 per group).

RESOURCES

ANALYSIS OF COVID-19 CLINICAL TRIALS: A DATA-DRIVEN, ONTOLOGY-BASED, AND NATURAL LANGUAGE PROCESSING APPROACH

Alag S.. PLoS One. 2020 Sep 30;15(9):e0239694. doi: 10.1371/journal.pone.0239694. eCollection 2020.
Level of Evidence: Other - Review / Literature Review

BLUF

This paper presents a resource developed by a high school student from The Harker School in San Jose, California who data mined ClinicalTrials.gov using Application Programming Interfaces (APIs) to compile relevant data from COVID-19 clinical trials (Figure 1) including drug treatments and interventions, outcomes, Medical Subject Heading (MeSH) (Figure 7), and Human Phenotype Ontologies (HPO) (Figure 8). The results (available at http://covidresearchtrials.com) provide a public compilation of unique reports in each category analyzed, which could offer guidance to the global research community to support development of future clinical trials, treatments and interventions, and meta-analyses, as well as general insight into the response to COVID-19.

ABSTRACT

With the novel COVID-19 pandemic disrupting and threatening the lives of millions, researchers and clinicians have been recently conducting clinical trials at an unprecedented rate to learn more about the virus and potential drugs/treatments/vaccines to treat its infection. As a result of the influx of clinical trials, researchers, clinicians, and the lay public, now more than ever, face a significant challenge in keeping up-to-date with the rapid rate of discoveries and advances. To remedy this problem, this research mined the ClinicalTrials.gov corpus to extract COVID-19 related clinical trials, produce unique reports to summarize findings and make the meta-data available via Application Programming Interfaces (APIs). Unique reports were created for each drug/intervention, Medical Subject Heading (MeSH) term, and Human Phenotype Ontology (HPO) term. These reports, which have been run over multiple time points, along with APIs to access meta-data, are freely available at http://covidresearchtrials.com. The pipeline, reports, association of COVID-19 clinical trials with MeSH and HPO terms, insights, public repository, APIs, and correlations produced are all novel in this work. The freely available, novel resources present up-to-date relevant biological information and insights in a robust, accessible manner, illustrating their invaluable potential to aid researchers overcome COVID-19 and save hundreds of thousands of lives.

FIGURES

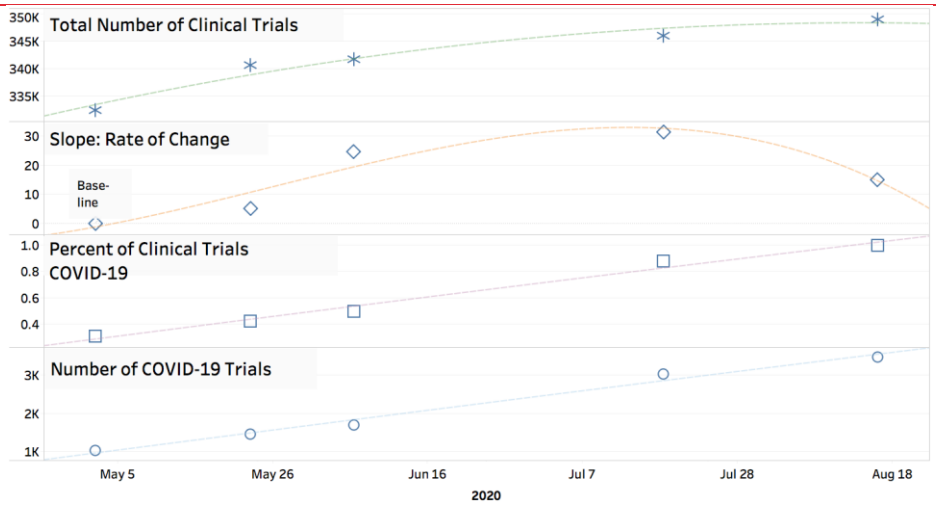

Figure 1. COVID-19 clinical trial trends: Longitudinal trends from COVID-19 related clinical trials. The data is plotted across five time points: May, 3rd 2020, May, 23rd, 2020, June 6th, 2020, July 18th, 2020, and August 16, 2020. (a) The total number of clinical trials at each time points; (b) Percent of new clinical trials (trials published between time segments) that are COVID-19 related; (c) Percent of all clinical trials that are COVID-19 related; (d) The total number of COVID-19 related clinical trials.

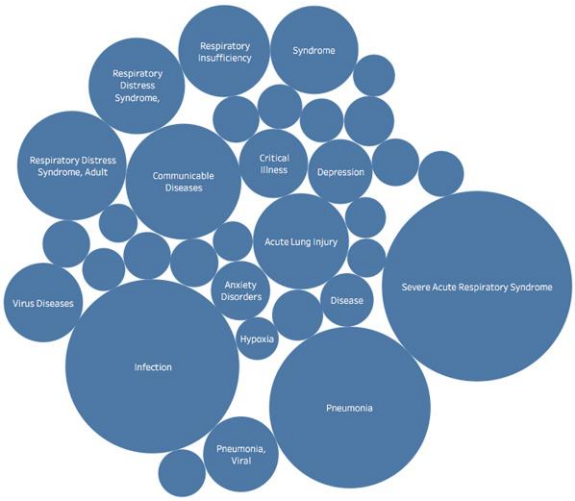

Figure 7. MeSH information details the most prevalent MeSH terms across COVID-19 related clinical trials. Some notable and expected prominent terms are Infections, Severe Acute Respiratory Syndrome, and Pneumonia.

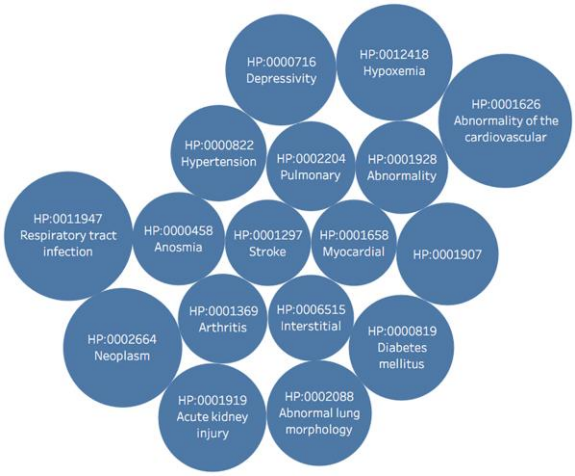

Figure 8. HPO information portrays the most widely noted HPO terms. Note that HPO terms are normalized as detailed in Alag 2020 [6]. The most frequent terms were Respiratory tract infection, Abnormality of the cardiovascular system, Acute kidney injury, Abnormal lung morphology, Depressivity, Diabetes mellitus, and more.

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