CanCOVID Issue Note

Biomarkers and ICU admissions among COVID-19 patients

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EXECUTIVE SUMMARY

Biomarkers and ICU admissions among COVID-19 patients

Question: which factors result in some infected individuals going into the ICU or not? Are there any predictive tools or biomarkers? Compounding of COVID-19 with co-morbidities.

Summary of Included Resources

From our rapid search, we identified four meta-analyses, one systematic review, and four relevant original studies, all of which focused on biomarkers and the severity, morbidity, mortality, and diagnosis of hospitalized COVID-19 patients. Studies included in the systematic reviews and meta-analyses were of low- to high-quality according to the authors' quality assessments. The comprehensiveness of this summary may be limited given the rapid timeline for our search and documents retrieved, and it is possible that we may have missed potentially relevant evidence.

What do we know?

Existing research identified a number of biomarkers that are associated with disease severity, and mortality among hospitalized COVID-19 patients and may help to predict need for ICU care. Early detection of identified biomarkers may improve patient management and help identify high-risk patients. Associations were found between COVID-19 disease severity and early biomarkers of inflammation and organ dysfunction including lymphopenia, thrombocytopenia, and elevated levels of D-dimer, C-reactive protein (CRP), Procalcitonin (PCT), Lactate Dehydrogenase (LDH) as well as high levels of cardiac troponin I and aspartate aminotransferase (AST). Furthermore, there is a strong association between increases in biomarkers including CRP, D-dimer, and decreased platelet count, and increased mortality. There are also prediction models that may be useful in identifying COVID-19 patients with high risk of death within two months. One model suggests that age, respiratory failure, white cell count, lymphocytes, platelets, D-dimer, and lactate dehydrogenase are key determinants of death among hospitalized COVID-19 patients. Comorbidities including diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease are associated with an increase in severe COVID-19 symptoms and mortality. Patients with hypertension, cerebrovascular accident, and heart disease may be at increased risk of needing ICU care, requiring intubation, and death.

What are the notable gaps?

Biomarkers associated with severe COVID disease and mortality identified to date, are general markers of inflammation and organ dysfunction, and not specific to COVID-19. COVID-specific biomarkers for severe disease and mortality have not yet been identified. Our search did not find higher-level evidence (i.e., evidence from systematic reviews, meta-analyses, or rapid reviews) focusing on biomarkers associated with ICU admission. Further research to identify biomarkers predictive of need for ICU level care is needed.

What is on the horizon? What are the studies that are underway to address the gaps?

There are various research projects funded across Canada investigating different approaches to predicting COVID-19 severity (including ICU admission) such as genetic biomarkers, immunologic markers, remote symptom monitoring, and mathematical modelling. These include:

- "Identification of Biomarkers that Predict Severity of Infection in COVID-19 Patients" (Melissa Kathryn Andrew, Dalhousie University)

- "Population-estimable frailty using "big data" to predict Covid-19 infection and illness severity, Institute of Clinical Evaluative Sciences" (Douglas Lee, Institute of Clinical Evaluation on Sciences, University of Toronto)
- "AI-empowered Real-time COVID-19 Symptom Monitoring and Prediction among Senior Residents" (Rahimi Samira, McGill University)
- "An Optimized COVID-19 Diagnostic Test Incorporating Host Responses for Predicting Disease Course and Healthcare Needs" (Jeremy Hirota, McMaster University)
- "CovidFree@Home: Development and validation of a multivariable prediction model of deterioration in patients diagnosed with COVID-19 who are managing at home" (Nisha Andany, Sunnybrook Research Institute)
- "Genomic biomarkers to predict outcome and treatment response in hospitalized COVID-19 patients" (Matthew Cheng, McGill University)
- "COVID-19: Comprehensive biomarker analysis for prediction of clinical course and patient treatment outcomes (COVID-BEACONS)" (Paul Y Kim, McMaster University)
- "Development of a Predictive Serologic Test for Cytopathogenic Autoantibodies in COVID-19 Patients" (Robert K. Rottapel, University Health Network)

There are also on-going reviews initiated internationally (Brazil, Germany, Belgium, Malaysia, China, India, Spain, and Italy) which address possible genetic, clinical, diagnostic, and sociodemographic predictors of COVID-19 outcomes and prognosis. One systematic review by Malaysian researcher Yean Yean Chan titled, *Impact of mutational profile of SARS-CoV-2 on transmissibility and disease severity: A systematic review and meta-analysis*, is looking to answer questions around whether there are associations between viral load levels and transmissibility and severity of illness.

Concluding statement: there are biomarkers and comorbidities that are associated with severe health outcomes of hospitalized COVID-19 patients that may lead to ICU admissions. However, higher-level evidence (i.e., evidence from systematic reviews, meta-analyses, or rapid reviews) focusing on the direct associations between biomarkers and ICU admission is lacking.

Which factors result in some infected individuals going into the ICU or not? Are there any predictive tools or biomarkers? Compounding of COVID-19 with co-morbidities.

The following presents the best available evidence retrieved from a rapid scan of the published literature using trusted sources in response to the above question. We found four meta-analyses, one systematic review and four single original studies. Due to the rapid timelines, it is possible that we may have missed potentially relevant evidence. Links to the source documents are included. The short summaries for each resource listed below provide an overview of the main results, usually found in the abstract and key summary/messages section. This scan does not include any further analysis or integration of results. The comprehensiveness of this summary may be limited given the rapid timeline for our search and documents retrieved, and it is possible that we may have missed potentially relevant evidence.

Table 1: References and brief summaries

Type of Evidence	Author	Resource	Last Updated	Summary
Meta-Analysis	Lippi et al.	Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis	July 2020	• Methods: authors conducted an electronic search in Medline, Scopus, and Web of Science and then conducted a meta-analysis. • This study found a lack of established laboratory markers available to evaluate illness severity of COVID-19. • It was determined that platelet count was significantly lower in patients with more severe COVID-19 and an even lower platelet count was observed with mortality. • Low platelet count is associated with risk of severe disease and mortality and can serve as clinical indicator of worsening illness due to COVID-19 during hospitalization.
Systematic review and meta-Analysis	Malik et al.	Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis	August 31, 2020	• Methods: authors conducted a systematic review and meta-analysis of observational studies. • Based on results from 32 different studies with a cumulative 10,491 COVID-19 patients, a significant association was found between severity of COVID-19 and lymphopenia, thrombocytopenia and elevated D-dimer, CRP, PCT, and LDH.

				• Determining these early biomarkers for COVID-19 can aid with management and identification of high risk COVID-19 patients.
Meta-Analysis	Toraih et al.	Association of cardiac biomarkers and comorbidities with increased mortality, severity, and cardiac injury in COVID-19 patients: A meta-regression and decision tree analysis	June 12, 2020	• Methods: authors conducted a systematic review and meta-analysis of retrospective, prospective, observational, descriptive, or case control studies published up until May 8, 2020. • This study aimed to identify the association between severity of COVID-19 and history of cardiovascular disease and/or comorbidities. • A meta-analysis of 17,794 patients showed that adverse outcomes of COVID-19 were associated with high levels of cardiac troponin I and aspartate aminotransferase. • Identification of cardiac injury biomarkers for patients with COVID-19 may help identify high risk patients and improve approaches to treatment.
Meta-Analysis	Singh et al.	Prevalence of co-morbidities and their association with mortality in patients with COVID-19: A systematic review and meta-analysis	June 23, 2020	• Methods: authors conducted a systematic review and meta-analysis. • Methods: this study assessed the association between comorbidities and risk of COVID-19 severity and mortality. It also aimed to estimate the prevalence of cardiometabolic and other comorbidities in COVID-19 patients. • Comorbidities assessed in 18 studies with a total of 14,558 patients included hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and cancer. • COVID-19 patients with the presence of diabetes, hypertension, cardiovascular disease, and chronic obstructive pulmonary disease are associated with about a two-fold increase in severe COVID-19 symptoms and mortality.

Systematic review	Kermali et al.	The role of biomarkers in diagnosis of COVID-19 – A systematic review	August, 2020	• Methods: authors conducted a systematic review of six different databases. • Increases in C-reactive protein (CRP) and D-dimers have strong associations with increased mortality. • Decreases in platelet count are strongly associated with mortality. • Lymphocytes and platelet count were significantly lower in severe patients compared to non-severe patients. • More research is needed to determine how information about these biomarkers can benefit clinicians in identifying severe disease earlier.
Single study	Mei et al.	Development and external validation of a COVID-19 mortality risk prediction algorithm: a multicentre retrospective cohort study	November 23, 2020	• Methods: multicentre retrospective cohort study of confirmed adult patients with COVID-19. • Methods: setting was five designated tertiary hospitals for COVID-19 in Hubei province, China. • Methods: authors conducted a multivariate logistic regression model with predictor variables to predict individual risk of short-term mortality after COVID-19 diagnosis, with predictors of age, respiratory failure, white cell count, lymphocytes, platelets, D-dimer, and lactate dehydrogenase. • Full mode included age, respiratory failure, white cell count, lymphocytes, platelets, D-dimer, and lactate dehydrogenase, and two interaction terms. • Simple model included age, respiratory failure, coronary heart disease, renal failure, heart failure, and one interaction term. • In the full model, increased risk of mortality was associated with respiratory failure (OR 53; 95%CI, 22 to 128). • Age, respiratory failure, white cell count, lymphocytes, platelets, D-dimer, and lactate dehydrogenase are key determinants of death after COVID-19 infection in the full model.

				• Authors conclude that their prediction models may be useful identifying COVID-19 patients with a high risk of death in 60 days.
Single study	Zhao et al.	Prediction model and risk scores of ICU admission and mortality in COVID-19	July 30, 2020	• Methods: authors conducted a retrospective study using clinical data at hospital admission. • Lactate dehydrogenase, procalcitonin, pulse oxygen saturation, smoking history and lymphocyte count were significant variables predicting ICU admission. • Heart failure, procalcitonin lactate dehydrogenase, chronic obstructive pulmonary disease, pulse oxygen saturation, heart rate and age were significant variables predicting death.
Single study	Hernández et al.	Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection	October 27, 2020	• Methods: authors conducted a retrospective case-control study. • Vitamin D-deficient COVID-19 patients had a greater prevalence of hypertension and cardiovascular diseases, as well as a longer hospital stay. • No causal relationship was found between vitamin D deficiency and COVID-19 severity. • Vitamin D levels are lower, and there is a higher level of deficiency in hospitalized COVID-19 patients compared to population-based controls.
Single study	Ayanian et al.	The Association Between Biomarkers and Clinical Outcomes in Novel Coronavirus (COVID-19) Pneumonia in a U.S. Cohort	May 29, 2020	• Methods: authors conducted a retrospective study of admitted patients. • Increased IL-6, D-dimer ferritin, C-reactive protein, and lactate dehydrogenase were found to be statistically significant and associated with higher odds of clinical deterioration and death. • Hypertension, cerebrovascular accident, and heart disease had increased risk of needing care in the ICU, requiring intubation and death. Chronic kidney disease was associated with death.

Table 2: Upcoming research related to ICU predictive factors and tools

Author (institution/country)	Title	Abstract/ Description	Source
Andrew, Melissa Kathryn ; Kelvin, Alyson Ann ; Kelvin, David J. ; Marshall, Jean Sylvia ; McNeil, Shelly Ann; Kozak, Robert Andrew ; McGeer, Allison Joan ; Mubareka, Samira (Dalhousie University)	Identification of Biomarkers that Predict Severity of Infection in COVID-19 Patients	The outbreak of the new coronavirus in Wuhan, China has infected over 75,000 people and has caused close to 2,000 deaths. One of the major problems with this outbreak is that emergency rooms, hospitals and ICU wards are overwhelmed with patients. In an effort to find a test for rapidly determining who should be admitted to the hospital and who should be placed in ICU, we have undertaken an international study to find a set of biomarkers that can be used to help Emergency Room doctors to make decisions on whether a patient will become severe. We have established an international team based in China, Vietnam, Spain, Italy, Mozambique, Sudan, Ethiopia, Egypt, Morocco, Cote D' Ivoire and Canada. This team will examine patients peripheral blood for biomarkers that predict the course of disease as mild or severe. The results of the study will be used to make a device that can be used in any situation and rapidly give results to predict the course of coronavirus infections.	Canadian Research Information System

Douglas Lee, Harindra Wijeysundera, Husam Abdel-Qadir, Peter Austin, Moira Kapral, Jeffrey Kwong , Peter Liu, Paula Rochon, Heather Ross, Louise Sun, Jacob Udell, Bo Wang. (Institute of Clinical Evaluation on Sciences, University of Toronto)	Population-estimable frailty using "big data" to predict Covid-19 infection and illness severity, Institute of Clinical Evaluative Sciences	Early studies have indicated that older persons are at high risk of severe COVID-19 infection, but it is not known if frailty is more important risk factor than age alone. It is important for older individuals to know if they are at increased risk of infection from COVID-19, to prevent delays in seeking medical care when early symptoms occur. In this study, we will determine if frailty is an important predictor of COVID-19 infection and adverse outcomes using 'big data' and artificial intelligence-based methods. We will also determine if patients that are frail were further impacted because of the restrictions to care that were imposed upon the population in response to the pandemic. Over the two-year duration of the proposal, our team of investigators will study health data on the population of all residents of Ontario, and determine the frailty status of all persons in the province. We will analyze COVID-19 testing data that is being collected right now, and available to the research team, linked to the hospitalization and vital status data available at ICES. We will collaborate with artificial intelligence researchers at the Vector Institute to determine if frailty and the other associated epiphenomena are also associated with COVID-19 infection and outcomes. We will compare access to virtual and ambulatory care for vulnerable, individuals that are frail during the Covid-19 pandemic using sophisticated statistical and temporal analyses. The knowledge that is gained from is important because we need to be better able to identify those who are at high risk during the first and subsequent waves of COVID-19. If frailty is a predictor, it can guide educational and preventative strategies to protect vulnerable individuals.	Canadian Frailty Network

Rahimi, Samira (McGill University)	AI-empowered Real-time COVID-19 Symptom Monitoring and Prediction among Senior Residents	Long-term care (LTC) homes are being disproportionately affected by COVID-19. This project will implement proven remote monitoring technology empowered with Artificial Intelligence to track, monitor and predict senior residents' symptoms. The detection and prediction of asymptomatic changes will facilitate rapid isolation and can save thousands of lives. The technology will alert the providers when COVID-19 symptoms are identified/predicted and monitor any decompensation. This project will monitor 60 senior residents in two LTC homes (Toronto and Montreal) and then scale up for the entire LTC homes, and intends to protect LTC home staff and frail residents from exposure to COVID-19 by enabling remote monitoring.	Roche Canada
Hirota, Jeremy (McMaster University)	An Optimized COVID-19 Diagnostic Test Incorporating Host Responses for Predicting Disease Course and Healthcare Needs	Understanding host immune responses to SARS-CoV-2 infection may yield prognostic indicators useful for optimizing healthcare delivery at the time of initial nasal swab collection for COVID-19 diagnosis. Nasal swabs are collected for COVID-19 clinical diagnosis, presenting a research opportunity to leverage remaining nucleic acids for host transcriptomic profiling and correlating with clinical outcomes. The objective is to correlate host transcriptome profiles from nasal swabs from COVID-19 +ve and -ve cases with clinical outcomes to generate algorithms for predicting patient morbidity/mortality and healthcare utilization, with the aim of optimizing COVID-19 diagnostic testing incorporating host responses.	Roche Canada
Andany, Nisha ; Chan, Adrienne ; Daneman, Nick ; Falk, Tiago H ; Gershon, Andrea Sara ; Lam, Philip Wai-Hei ; Masood, Sameer ; Rudzicz, Frank ; Simor, Andrew Eugene ; To, Teresa ; Wu, Robert ; de Lara, Eyal.	CovidFree@Home: Development and validation of a multivariable prediction model of deterioration in patients diagnosed with COVID-19 who are managing at home	Millions of Canadians are anticipated to be infected with COVID-19 during this pandemic and many more will contract it in ongoing community transmission and/or a possible second wave. The majority of people who test positive for COVID-19 are sent home to	Canadian Research Information System

(Sunnybrook Research Institute)		isolate. In this population, deterioration of their disease can happen quickly and without warning, and we currently cannot accurately predict the approximately 20% who deteriorate and need hospitalization. From discussions with our patients and patient advisor, we know that people who are isolating at home feel terrified and alone. We need an effective and safe ambulatory care and research strategy for people with COVID-19 isolating at home. We are a team of heath care workers, patients, researchers and computer scientists (WearCOPD.ca; Can-BREATHE.ca) with five years of experience developing and using remote monitoring systems for respiratory disease. We have already built a smartphone application to facilitate the care of people with COVID-19 at home by allowing them to report their symptoms to their physician. With this project, we will expand our system to also include continuous smartwatch-based monitoring of heart rate, respiratory rate, cough, speech and other parameters. Sensor data will provide us with large volumes of objective data and allow us to build accurate real time machine learning models for predicting who needs to go to hospital. We will integrate these models into a dashboard that alerts clinicians of any patients that area getting worse, so that they can be called into hospital. Patients can be reassured that they are being followed thoroughly even though they are at home. Our system will also provide a platform for further research into how to prevent long term sequalae and preserve the health of people with COVID-19 who do not require hospitalization.	

Matthew Cheng, Erwin Schurr, Guillaume Bourque (McGill University)	Genomic biomarkers to predict outcome and treatment response in hospitalized COVID-19 patients		[McGill University Faculty of Medicine and Health Sciences Website](#)
Kim, Paul Y ; Yeh, Calvin H; Fox-Robichaud, Alison Elizabeth ; Gross, Peter Lawrence ; Karkouti, Keyvan ; Kretz, Colin Andrew ; Liaw, Patricia C.Y. ; Mccluskey, Stuart Andrew ; Trigatti, Bernardo Louis ; Weitz, Jeffrey I. ; Werstuck, Geoffrey Hamilton. (McMaster University)	COVID-19: Comprehensive biomarker analysis for prediction of clinical course and patient treatment outcomes (COVID-BEACONS)	The COVID-19 pandemic has taken the world by storm. In Canada alone, there are more than 60,000 confirmed cases and more than 5,000 deaths. Despite its global impact, there are no specific therapies. While most patients display mild or no symptoms, a significant number result in severe disease, and sometimes death. We do not know what causes some patients to die from the infection. Developing a test that can identify patients who are at high risk of severe disease would help save lives. Early clinical reports noted that COVID-19 patients have a high risk of developing blood clots in the body including in the brain and lungs, thus hinting at how it makes people ill. We believe that this likely stems from a severe immune response to being exposed to the virus, SARS-CoV-2. This inappropriate response leads to a vicious cycle of damage to the blood vessels. Therefore, measuring when and how clotting problems develop may allow us to learn how severe COVID-19 disease progresses, find new treatment targets, and identify the patients that need to be treated earlier to prevent progression. To achieve this, we have assembled a collaborative effort between the largest intensive care hospital networks in Canada with the Thrombosis and Atherosclerosis Research Institute (TaARI), the largest and most comprehensive Canadian facility dedicated to the study of	[Canada Research Information System](#)

		inflammation and blood clotting diseases. We will measure biomarkers from the biological pathways that control inflammation, blood vessel integrity, blood clotting, and blood clot breakdown. We will then identify which markers can predict disease progression. By understanding which pathways are disrupted over the development of severe COVID-19 disease, we may be able to identify those patients requiring aggressive therapy earlier in the course of the disease.	

| Rottapel, Robert K. (University Health Network) | Development of a Predictive Serologic Test for Cytopathogenic Autoantibodies in COVID-19 Patients | Patients infected with the SARS-COV2 virus experience large variation in their clinical outcome. Most patients are asymptomatic or have mild symptoms while a smaller fraction of individuals develop devastating organ damage with fatal results. Currently, we have little insight into the factors that contribute to these dramatically different clinical outcomes. This proposal seeks to develop a test that will predict patients who may develop poor outcomes by measuring the emergence of antibodies that are destructive to tissues. These "destructive" antibodies are called autoantibodies. Normally our immune system generate antibodies protect us from viral and bacterial infections. We present preliminary data derived from a small cohort of COVID-19 patients that demonstrates the presence of autoantibodies in as many as 40% of infected patients. In some case these autoantibodies are present at high concentration. We will measure the presence of autoantibodies prospectively in a cohort of 150 patients that react against human lung cells, blood vessel cells and heart cells. The presence of these autoantibodies will then be correlated with the clinical course of Covid-19 infected patients. We will use well established mass spectroscopy methodologies to identify the proteins on human cells that are recognized by these autoantibodies. We will determine if purified autoantibodies from patients cause cell damage or death. Lastly, we will raise antibodies in mice directed against the proteins recognized by COVID-19 autoantibodies and determine if they cause injury to lung, heart, or blood vessels in animals. These efforts will allow us to develop a test to identify the emergence of autoantibodies in COVID-19 patients that will | Canada Research Information System |

		aid in stratification and the application of anti-viral therapeutics for those patients predicted to have unfavourable outcomes.	

Zhufeng Wang, Mei Jiang, Hongsheng Deng, Changxing Ou, Jingyi Liang, Yingzhi Wang (China)	Clinical symptoms, comorbidities and complications features in severe and non-severe patients with COVID-19: a systematic review and meta-analysis without cases duplication	What are the comorbidities, clinical symptoms and complications in severe and non-severe COVID-19 patients?	PROSPERO

Renan Souza, Diego Bonfim, João de Araújo, Renato de Aguiar (Brazil)	Host genetic variants associated with COVID-19 prognosis: a systematic review and metaanalysis	What are the host genetic variants associated with COVID-19 prognosis?	PROSPERO

Caterina Monti, Davide Capra, Massimo Cressoni, Simone Schiaffino, Isabella Castiglioni, Francesco Sardanelli (Italy)	Applications of artificial intelligence on chest x-ray for outcome prediction in COVID-19 patients	P (Population): COVID-19 patients I (Intervention): Application of artificial intelligence for the analysis of chest x-ray images C (Comparator): Not applicable O (Outcome): Prediction of clinical outcome	PROSPERO

Karanvir Kaushal, Manpreet Kaur, Subodh Kumar, Ajay Prakash (India)	Serum Ferritin as a predictor of occurrence, disease severity and clinical outcome in COVID-19. A systematic review, meta-analysis and meta-regression of observational studies	How the serum ferritin levels are associated with the disease severity and clinical outcomes of COVID-19?	PROSPERO

Esteban Obrero-Gaitan, Rafael Lomas-Vega, Irene Cortés-Pérez (Spain)	An overview of systematic reviews about sociodemographic factors and comorbidities that predict the severity and mortality from COVID-19	What are the sociodemographic and comorbidity factors that increase the impact of the disease and the risk of death in patients with COVID-19?	PROSPERO

Claudia Denkinger, Stephan Katzenschlager, Claudius Gottschalk, Juergen Grafeneder, Markus Weigand, Lena Maier-Hein, Alex Seitel (Germany)	A systematic review of the clinical and laboratory indicators that predict hospitalisation, intensive care admission, intubation and mortality in patients with COVID-19 disease	What are the clinical and laboratory indicators that predict hospitalization, intensive care admission, intubation and mortality in patients with COVID-19 disease?	PROSPERO

Jessica Da Silva Campos, Jessica Barletto de Sousa Barros (Brazil)	Genetic polymorphisms associated with worse progression of COVID-19 in diabetes mellitus patients: systematic review and meta-analysis	What are the genetic polymorphisms that are associated with the worst outcome of COVID-19 in patients with diabetes mellitus?	PROSPERO

Andrea Cozzi, Marco Alì, Massimo Cressoni, Simone Schiaffino, Isabella Castiglioni, Francesco Sardanelli (Italy)	Applications of artificial intelligence on computed tomography for outcome prediction in COVID-19 patients	P (Population): COVID-19 patients I (Intervention): Application of artificial intelligence for the analysis of computed tomography images C (Comparator): Not applicable O (Outcome): Prediction of clinical outcome	PROSPERO

Charlotte Beaudart, Anh Nguyet Diep, Médéa Locquet, Christian Brabant (Belgium)	Prediction models for the diagnosis of COVID-19 in hospital setting: a systematic review	"What are the set of diagnostic models, published in the scientific literature, for predicting the positivity or not of covid-19 in hospital setting and how do they perform when comparing them head-to-head, what is the optimal diagnostic model?"	PROSPERO

Yean Yean Chan, Zaidah Abdul Rahman, Azian Harun, Engku Nur Syafirah Engku Abd Rahman, Yusuf Wada, Muhammad Fazli Khalid, Nur Fadhlina Musa, Rosline Hassan, Wardah Yusof, Ahmad Adebayo Irekeola (Malaysia)	Impact of mutational profile of SARS-CoV-2 on transmissibility and disease severity: A systematic review and meta-analysis	- How does global SARS-CoV-2 mutations dynamic impact on transmission properties or superspreading characteristics and severity of illness of the COVID-19 disease? - What are the mutations that occur in SARS-CoV-2 and what are their prevalence? Secondary questions: - Is there any association between the mutation points and severity of illness? - Is there an association between viral load levels and the transmissibility? - Is there an association between viral load levels and the severity of illness? - Is there any association between the duration of viral shedding and transmissibility?	PROSPERO