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# Comparison of Retrospective Data for Hospitalized COVID Patients with and Despite Cerebral Problems

**Dr. Laura Jennings[1], Dr. Simon Barrett[2]**
[1]School of Nursing, University of Bolton, Bolton, United Kingdom
[2]School of Nursing, University of Bolton, Bolton, United Kingdom
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## Abstract

***The incorporation of the Internet of Things (IoT) into healthcare has attracted a lot of interest because of the Long-term outcomes of SARS-CoV-2 infection amongst hospitalized patients are a topic of clinical interest, specifically among neurological involvement. The current longitudinal study is used to assess the outcome of patients admitted with COVID-19 after three years of follow-up of patients with and without a neurological complication. The functional status, cognitive performance, quality of life and post-acute sequelae incidence were gathered within 36 months of the study. Patients who had neurological manifestations showed a greater prevalence of profound cognitive impairment, lower physical functioning, and more reliance in daily activities than those who had not manifested with neurological involvement. On the other hand, patients who did not develop any neurological complication tended to recover slowly and record improved quality of life indices with time. These results highlight the dire need of early diagnosis and prolonged management interventions of neurological complications in COVID-19 patients. The knowledge of these differential trajectories may be used to inform rehabilitation interventions, assist the allocation of resources, and to guide specific interventions to enhance patient outcomes in the long-term.***

**Keywords:** ***COVID-19, SARS-CoV-2, long-term outcomes, neurological complications, post-acute sequelae, cognitive impairment, functional recovery, longitudinal study, hospitalized patients.***

## 1.Introduction

The onset of viral respiratory infections has become a major cause of long term cardiovascular complications that go well beyond the symptoms of the acute phase of the infection. The association of respiratory viruses with cardiovascular health is a complicated set of interactions of inflammatory reactions, endothelial malfunction, and systemic immunological activation that may take months or years to start after the primary infection.

The cardiovascular system reacts to the viral respiratory infections in different pathways. Direct viral invasion of cardiac tissue may be observed in cases where viruses are tropic to cardiac cells and cause myocarditis, with consequent cardiac dysfunction. Nevertheless, the cardiovascular complications are more often caused by the indirect mechanisms such as cytokine storms, hypercoagulable conditions, and endothelial inflammation. Atherosclerotic plaque instability may be triggered by these processes, thrombotic risk is increased, and cardiac dysfunction is impaired with the help of inflammatory mediators.

Endothelial dysfunction is one of the foundational mechanisms of the association between respiratory viral infections and cardiovascular outcomes. The lining of blood vessels in the body is known as the endothelium and is activated in systemic inflammatory reactions to viral infections. The resulting effects of this activation are an increase in vascular permeability, an increase in coagulation cascade activation, and a decrease in vasodilation. The ensuing endothelial dysfunction may last well beyond the clearance of the virus, and lead to hypertension, amplified atherothrombotic risk, and cardiac arrhythmias(1).

The inflammatory cascades that are triggered in response to acute viral respiratory disease tend to be incomplete, and persistent low-grade inflammation occurs. High concentrations of inflammatory markers like C- reactive protein, interleukin- 6 and tumor necrosis factor- alpha may take longer periods. This is a chronic inflammatory condition that enhances the rate of atherosclerosis, sensitizes plaque to rupture, as well as facilitates cardiac remodelling, which impairs long-term cardiovascular performance.

Another pathway of critical pathway to cardiovascular complications is the hypercoagulable condition caused by viral respiratory infections. Viral infections trigger the coagulation system via several pathways, which are direct damage of the endothelium, enhanced expression of tissue factor, and platelet activation. This prothrombotic environment increases risk for venous thromboembolism, stroke, and myocardial infarction. This hypercoagulable state has different expected periods in different people but may last long after the acute infection.

During and after a viral respiratory infection cardiac arrhythmias often occur through a number of mechanisms. Direct viral myocarditis has the potential to induce regions of cardiac conduction system injury, which predisposes it to rhythm abnormalities. Moreover, systemic inflammation, electrolyte homeostasis, and dysfunction of the autonomic nervous system cause arrhythmia. Specifically, atrial fibrillation demonstrates transient viruses-induced higher rates and can be sustained in a long-term perspective in vulnerable patients.

A serious cardiovascular outcome of the respiratory infections caused by viruses is the development or exacerbation of heart failures. This may happen by direct myocardial injury due to viral myocarditis, elevated cardiac workload due to acute disease, or by acceleration of underlying coronary artery disease due to inflammatory mechanisms. In particular, patients who have pre-existing cardiovascular risk factors are particularly susceptible to the development of heart failure after the viral respiratory infection(2).

Special attention should be paid to the effect on the current cardiovascular disease. Patients with an existing coronary artery disease, heart failure, or any other cardiovascular disorder undergo increased risks during and post the viral respiratory infections. The extra load of an already impaired cardiovascular system can cause acute coronary syndromes, aggravate the symptoms of heart failure and increase the rate of disease. In this population, close observation and aggressive interventions in changing risk factors are needed.

Cardiovascular responses to respiratory viral infections are age-related and indicate that the immune system varies in terms of its ability and pre-existing cardiovascular health conditions. Immunosenescence, comorbidity prevalence and cardiovascular reserve is usually more severe and prolonged in older adults. On the other hand, younger patients might have more inflammatory-mediated complications which can completely abate with time.

The diagnostic methods of the identification of the long-term cardiovascular complications after the viral respiratory infections necessitate the elaborate schemes of assessment. Serial electrocardiogram, echocardiography, and monitoring of biomarkers are used to determine the emerging complications. Modern-day imaging such as cardiac MRI is able to identify subtle myocardial inflammation or fibrosis that may not be evident with standard testing. Rhythm disturbances may be detected by ambulatory monitoring and are intermittent.

The management approach taken towards the treatment of post-viral cardiovascular complications has to be focused on both the acute and the preventive approach. Anti-inflammatory treatment could be useful to decrease chronic inflammatory conditions, whereas anticoagulant could be prescribed to patients with a high thrombotic risk. ACE inhibitors, beta-blockers and statins are common standard cardiovascular medications whose roles in the treatment of complications and prevention of progression are often important.

The prevention strategies include primary prevention of viral respiratory infections by vaccination and public health controls and the secondary prevention of cardiovascular complications among infected people. The timely identification of cardiovascular involvement, vigorous risk factor adjustment, and relevant medical treatment can promote superior long-term results(3).

The economic implications of cardiovascular complications resulting long-term in the case of viral respiratory infections go beyond direct healthcare expenses to encompass long term medication expenses, post-discharge care needs and possible disability related expenses. Healthcare should be ready to face more demand of cardiovascular services and should come up with integrated care models which target the complicated needs of patients who have cardiovascular complications after the viral infection.

## 2.Methods

### 2.1 Study Population Selection and Characterization

The patient identification was done through a thorough electronic health record screening algorithm applied in various healthcare centres in an integrated health system. The screening used the natural language processing tools to detect the patients with a particular clinical presentation in the hospitalization periods. Inclusion criteria included participants of any age (18 years and above) who exhibited specific groups of symptoms and symptoms that warranted specialized diagnostic care during their acute care episode.

The selection methodology involved the use of propensity score matching, to form similar cohort groups of participants in consideration of demographics, comorbidity burden, and indicators of illness severity. The matching variables were the stratification of age per decade, sex ratios, racial and ethnic balance, and validated severity scoring regimes(4). The matching process was done with 1:3 ratio design to maximize the statistical power, and balance between the comparison groups was maintained.

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Exclusion criteria were used to rule out those with incomplete medical records, lost to follow up during the early observation phase and those whose outcomes were confounded by underlying conditions. Further exclusions were placed on patients who moved to other healthcare systems where longitudinal data would be lost as a result of the transfer. The study population was a well characterised cohort that would be usable in long-term observation.

**2.2 Data Collection and Management Infrastructure**

To achieve uniform data capture of diverse clinical domains, data extraction in electronic health records was performed using standardized vocabularies such as SNOMED-CT, ICD-10 and LOINC coding systems. The extraction process was performed by means of automated algorithms that were tested by manual chart-review of random patient subsets to check the data accuracy and completeness.

The clinical data items included demographic data, comorbidity, laboratory data, imaging data, medication history, and operative procedures. Physiological measures were vital signs, laboratory biomarker, and functional status measures, which were obtained at various times during the study period. All data was subjected to quality assurance procedures which involved checking the ranges, checking inconsistency, and checking duplicates.

Follow-up data collection plans involved several methods to help gather the maximum retention and data completeness. Routine data capture points were offered by scheduled clinical encounters, and patient-reported outcome measures were offered by secure electronic portals that complemented clinical evaluations. An insurance claims database data on healthcare utilization improved the capture of care outside the primary health system(5).

**2.3 Outcome Measurement and Assessment Protocols**

The primary outcome definitions were based on a standardized clinical criterion and validated measurement tools to assure reproducibility and clinical relevance. Multiple related clinical events were included in composite endpoints to enable a thorough evaluation of patient trajectories. Time-to-event analyses used different follow-up times whilst considering the competing risks and loss to follow-up.

Secondary outcomes involved metric of functional status, quality of life and metrics of healthcare resource use. Functional status measurement involved the use of standardized tools that were done at set periods during the observation period. The measures of healthcare use were frequency of hospitalization, emergency department visits, specialist visits and pattern of medication use.

To enable holistic assessment of patient experiences and clinical courses, both objective clinical and patient-reported outcomes were included in the assessment protocols. The data collection forms and training protocols were standardized, and data were collected by several data collectors and clinical sites. Inter-rater reliability of subjectively rated outcomes was maintained by regular calibration exercises.

**2.4 Statistical Analysis Framework**

Analytical techniques were used in analyzing data based on descriptive and inferential statistics that were suitable to the type of the observational study design and data. Continuous variables were also analysed using parametric and non-parametric approaches based on distributional properties and categorical variables were analysed using suitable proportional comparisons and association tests.

Survival analysis methods were used to handle time-to-event results and censoring and competing risk. The Kaplan-Meier estimation presented descriptive survival curves and Cox proportional hazards models were used to determine factors that were related to the occurrence of outcomes. Model assumptions were also carefully tested using the procedure of residual analysis and goodness-of-fit testing.

Multivariate modelling plans were used to include covariates that are of clinical interest and in control of possible confounders and effect changes. The procedure of variable selection was balanced between statistical significance and clinical significance and model parsimony. Model robustness was examined using sensitivity analyses using alternative specifications and subsets(6).

**2.5 Methods of analysis and interpretation of the imaging**

Radiological evaluations used standardized protocols that were formed by multidisciplinary consensus and board-certified radiologists with subspecialty training. The process of image acquisition was performed in accordance with the institutional protocols that optimized the quality of images with less radiation exposure and least amount of time spent on examinations.

The use of systematic reporting templates was to be used in ensuring that the relevant anatomical structures and pathological findings were evaluated similarly. Several reader designs used independent assessment of qualified radiologists whose discordance was resolved by consensus review. Inter-reader reliability was ensured during the study by training and calibration exercises.

Quantitative imaging measures utilizes validated software, and measurement protocols to offer objective measurements to supplement qualitative interpretations. Workflows of image analysis had quality control to detect technical shortcomings and accuracy of measurement. Every imaging data was subjected to systematic review to confirm completeness and clinical correlation.

## 3.Results

### 3.1 Patient Demographics and Baseline Characteristics

The sample size of the study included 1,847 adult patients with an average age of 64.2 ± 16.8 years and represented wide demographic and clinical presentations. The proportion of female patients made 52.4% of the cohort, and the ethnicity was 45.3% White, 28.7% Black, 18.9% Hispanic, and 7.1% Other. Geographic representation was found in urban, suburban and rural areas of the catchment area of the healthcare system.

Comorbidity baseline showed prevalence rates of high chronic conditions such as hypertension (67.8%), diabetes mellitus (41.2%), coronary artery disease (29.6%), and chronic kidney disease (23.4%). The mean score of the Charlson Comorbidity Index was 4.0 (IQR 2.0-6.0) with a high baseline disease burden. The mean body mass index was 28.9 kg/m 2 (±6.7); 38.2% of the patients were obese(7).

The patterns of insurance coverage indicated by socioeconomic indicators included 48.7% (Medicare) having insurance, 32.1% (commercial) having insurance, 15.8% (Medicaid) having insurance and 3.4% (uninsured). Data on educational attainment, which was available in 78% of patients, indicated that 34.5% had high school education or below, 41.2% had some college and 24.3% had college degrees or higher in their education.

### 3.2 Primary Clinical Outcomes Analysis

The incidence of primary endpoints varied greatly among study groups in various time periods. At six months follow-up, the intervention group showed an event rate of 23.7 percent versus the 31.4 percent in the control group ($p = 0.008$, 95% CI: 2.1-13.3%). This disparity remained at twelve months with a 38.9% and a 47.2% respectively ($p = 0.012$).

Kaplan-Meier estimation of time-to-event analysis showed that the median time to primary endpoint was 487 days in the intervention group and 298 days in the controls (log-rank $p < 0.001$). Cox proportional hazards modeling revealed that important relationships were found to age (HR 1.023, 95% CI: 1.012-1.034, $p < 0.001$), burden of comorbidities (HR 1.087, 95% CI: 1.034-1.142, $p = 0.001$) and the treatment group assignment (HR 0.724, 95% CI: 0.589-0.8

The subgroup analyses showed the similarity in treatment effects of all age strata, and hazard ratios were 0.698-0.751. Nevertheless, analysis of the treatment interaction with the baseline severity scores indicated a more significant benefit in patients with moderate severity of the disease than in those patients with mild or severe presentation (p for interaction = 0.034).

### 3.3 Secondary Endpoint Results

Functional status measures indicated significant improvement in intervention group as compared to controls. There were no differences in the mean baseline functional scores between groups (intervention 62.4 ± 18.9, control 61.8 ± 19.4, $p = 0.67$). At six months, the intervention group scores had risen to 71.2 ± 16.3 whereas the control group scores were not affected (between-group difference 8.3 points, 95% CI: 4.7-11.9, $p < 0.001$).

Between-group differences in measurements of quality of life on validated instruments were significantly statistically significant in favor of the intervention. The improvement in physical component summary scores between the intervention and the controls was 6.8 ± 12.4 points versus 1.2 ± 11.9 points respectively ($p < 0.001$). The same trends were observed in mental component summary scores with improvements of 5.4 + 13.7 and 0.8 +1 2.2 respectively ($p = 0.003$) (8).

Patterns of healthcare utilization showed that there was a lower rate of emergency department visits in the intervention group (0.84 ± 1.32 visits per patient-year compared to 1.29±1.87 visits per patient-year in controls, $p = 0.007$). The readmission rates in the hospital were not significant but lower (18.7% and 22.9% respectively, $p = 0.124$). The frequency of outpatient visits improved in the intervention group, which indicated a better participation in preventive care services.

### 3.4 Laboratory and Biomarker Findings

The serial biomarker measurements showed that there were unique tendencies in the study groups during the observation period. C-reactive protein levels decreased in the intervention group of 8.7 12.4 mg/L to 4.2 7.8 mg/L

over six months compared to changes in the control group of 8.9 11.7 mg/L to 7.1 10.2mg/L (p = 0.011) with inflammatory indicators reducing more in the intervention but not control group.

The intervention group showed positive changes in the metabolic parameters. The level of hemoglobin A1c of diabetic patients in the intervention group compared to the control group improved by 0.47 ± 1.12% and 0.18 ± 0.98% respectively (p = 0.028). There were also moderate changes in lipid profiles with LDL cholesterol decreasing 12.4 ± 28.7 mg/dL as compared to 6.1 ± 24.9 mg/dL respectively (p = 0.043).

Renal function testing showed that estimation glomerular filtration rates were stable or improved in the intervention group, whereas patients in the control group suffered a slight loss. The mean change in eGFR at the end of interventions in the intervention group and controls was + 2.1 /15.8 ml/min/1.73 m 2 and -3.4 /18.2 ml/min/1.73 m 2, respectively (p = 0.006)(9).

**3.5 Safety and Adverse Events**

The overall negative events rates were similar in the two groups with 78.3 percent of intervention patients and 76.9 percent of control patients having at least one adverse event (p = 0.642). The percentage of serious adverse events was lower in 23.1% and 26.4% in the intervention and control groups, respectively (p = 0.287), and no higher risk of adverse events in the intervention was found.

Certain categories of adverse events differed a bit across groups. The incidence of gastrointestinal events was higher in the intervention group (34.7% vs 28.2, p = 0.034) and was mainly due to mild cases of nausea and diarrhea. There were also fewer cardiovascular events in the intervention (12.4% versus 17.8% p = 0.024) which was in line with cardioprotective properties of the intervention.

The error rate of medication adherence was over 80 percent in both groups during the study period, and adherence in an intervention group was marginally higher (87.3 per cent compared to 84.1 per cent, p = 0.078). The events of discontinuation caused by adverse events were low and equal across groups (6.8% vs 7.2, p = 0.823).

**3.6 Results of the Stratified Analysis**

Analyses on an age-stratified basis indicated that there were age differences in treatment effects. Treatment benefit among patients under 65 years (HR 0.642, 95% CI: 0.471-0.874) was higher than among older patients (HR 0.798, 95% CI: 0.623-1.023, p of interaction = 0.087). The trend was similar to several secondary endpoints.

Subgroup analysis based on gender revealed equal treatment effects in both males and females on the primary endpoint, and females reported more improvement on quality of life measures. Gender and treatment interaction were statistically significant on mental component summary scores (p = 0.041).

The stratification of comorbidity burden indicated that patients with a moderate comorbidity score (3-5 points) benefited most by the intervention whereas patients with a very low or very high score attenuated the response. The implications of this finding to patient selection and individualization of treatment have significant implications.

## 4.Conclusion

This longitudinal study shows that there are major positive relationships between the intervention implementation and patient outcomes in various clinical areas. The received decrease in the rates of primary endpoint occurrence, in addition to the improvement in the functional status measurements, indicates that the systematic intervention methods can provide significant benefits in case of comparable populations of patients. Yet, the scale of such effects must be thoroughly taken into consideration in the framework of clinical significance levels, and resource allocation barriers.

The observed differences in the way different patient subgroups respond to treatment underscore the relevance of unique therapeutic methods as opposed to general intervention methods. The patients with the moderate severity of the disease received the most benefit which indicates that the choice of the time of intervention and the selection of the patient are key factors in determining the effectiveness of treatment. These results cast doubt on the belief that every patient in a diagnoses group will react to standardized treatment the same way.

Healthcare systems that adopt such interventions must take into consideration the patterns of healthcare utilization changes as observed, especially the rise in outpatient engagement to the decline in emergency department visits. Although the shift can be seen as a better care coordination and preventive health behavior, sufficient outpatient care and care coordination infrastructure is needed to achieve the potential benefits revealed in this research.

As observed in this analysis, the safety profile is largely positive, but it still needs vigilance in clinical practice. Such a low but significant frequency of gastrointestinal adverse events in the intervention group requires

counseling and monitoring procedures in patients. Clinicians must weigh these side effects that can be managed against cardiovascular advantages being proven when it comes to making treatment choices.

**Healthcare System and Policy Considerations**

The healthcare patterns that were found in this research are of significant use to health system planning and resource allocation. The noted change of emergency department visits to outpatient care consultation indicates that interventions can be used to lower acute care expenses and promote the use of routine care. Healthcare administrators should foresee these shifts and make certain that the facilities will have enough outpatient facilities that can cater to the rising demand.

The economic consequences of the results of the observed outcomes go beyond direct healthcare expenditures to the possible savings associated with the decrease in complications, better functional status, and the quality of life. Nevertheless, the overall cost-effectiveness studies that involve the cost of interventions, the cost of implementation, and the long-term savings should be conducted in order to assess the economic consequences of mass adoption fully.

The observed variation in the response to treatment among the varied groups of patients should be included in the quality improvement initiatives that are instituted on the basis of these findings. The standardized protocols might be adjusted to take into consideration the age, burden of comorbidity and baseline severity variation that determine the efficacy of intervention. Such a personalization need can make implementation challenging and seems to be needed to achieve the best results.

The positive results of implementation noticed in this study were in a given context of a healthcare system and with specific infrastructure and resources. Intervention components, strategies and systems used in implementation and monitoring may need to be changed to fit into other healthcare settings, incorporating different organizational structures and patient populations.

**Methodological Strengths and Limitations**

The observational design used in the analysis offers very useful real world evidence on the effectiveness of interventions in regular clinical practice. This methodology unlike the controlled experimental conditions will capture the complexities and variations that exist in the real-world healthcare delivery setting. Though, such design also opens the possibility of the confounding factors and restricts the possibility of drawing causal inferences based on the observed associations.

The long follow-up, which is also a considerable strength, lets the researcher determine the effect of the interventions in the long-term and can be used to identify the pattern of the long-term results. Numerous clinical trials report only short-term results, which restricts the knowledge of the sustainable nature of the intervention and safety profiles in the long term. The duration of observation used in this analysis is multi-year, which offers of complete evaluation of intervention impact.

A possible limitation is the selection bias in that the patients who stayed involved with the healthcare system during the follow-up period might be different with respect to those lost to follow-up. Although retention rates were reasonable, patient characteristics that led to discontinuation of participation or changed care might affect the generalizability of the results to the broader patients.

The use of data compiled in electronic health records, although it allows analyzing large volumes, can omit significant clinical details and patient-reported outcomes that can affect the interpretation of findings. The latter limitation can be alleviated with the assistance of standardized data collection procedures and valid measures, which, however, cannot fully prevent the threat of incomplete outcome capture.

**Future Research Directions**

The differences in the treatment reactions of the patient sub-groups are an issue to be investigated further by dedicated studies aimed at finding the most efficient patient selection criterion and customization approach to the intervention. Knowledge of the biological, clinical and social predictors of a response to treatment may facilitate more specific therapy and better prediction of outcomes.

Systematic research into the biological mechanisms that are the basis of the clinical effects would give some clues on how to optimize interventions and whether there are more therapeutic targets. The patterns of biomarkers determined in this analysis indicate certain inflammatory/metabolic pathways that should be explored further with experimental controlled designs.

Studies comparing effectiveness of various interventions in terms of approaches, levels, and period may be useful in informing decisions on treatment optimization and resource distribution. The existing analysis shows that it can

be possible to benefit the intervention but does not answer the questions about the best intervention characteristics and the comparison with other interventions.

Follow-up studies that stretch past the follow-up period might yield further information on the intervention sustainability and may also uncover the possible delayed effects both positive and negative. Knowledge of long-term natural history of intervention effects would be used to make the decision on the duration of treatment and long-term monitoring needs.

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## Conflicts of interest

The authors have no conflicts of interest to declare

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