**CCU002-04: TO COMPARE THE LONG-TERM RISK OF STROKE/MI IN PATIENTS AFTER CORONAVIRUS INFECTION WITH OTHER RESPIRATORY INFECTIONS – WELSH PROTOCOL**

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**BACKGROUND**

COVID-19 is primarily a respiratory disease (1). However, it is also a systemic illness with the widespread expression of angiotensin-converting enzyme-2 in infected individuals leading to prothrombotic and hyperinflammation (2, 3). Thus, this severe viral infection may increase the risk of serious cardiovascular diseases. Any elevated risk of cardiovascular disease after SARS-CoV-2 infection needs to be put into the context of risk after other acute viral infections, such as influenza or pneumonia, to allow a better understanding of the COVID-19 specific mechanisms that lead to complications such as stroke, myocardial infarction, pulmonary embolism, and deep vein thrombosis, and to understand the relative burden of cardiovascular disease (CVD) after COVID-19. This work will be an important contribution to our understanding of the clinical relevance of any endothelial or systemic inflammation associated with infection and have implications for new effective prevention strategies including therapeutic targets.

The inflammatory responses to COVID-19 may make underlying cardiovascular disease more likely to manifest (4). The comparison between COVID-19 and other respiratory infections will allow us to assess whether COVID-19 is associated with an elevated risk of adverse CVD outcomes above and beyond that of other respiratory infections and to show whether the high-risk periods are different between COVID-19 and viral influenza or pneumonia (non-COVID+) infections to better define when precautions are most effective. Our aims are the following 1) to quantify if the risk of cardiovascular diseases after COVID-19 infection is higher than non-COVID+ infection in general or in particular populations, 2) define whether the increased risk persists longer with COVID-19 than non-COVID+ infection, 3) to understand whether subsequent risk varies according to whether patients infected with COVID-19 or non-COVID+ are hospitalised or not hospitalised.

**PREVIOUS STUDIES**

* In a population-based cohort study of 2,647,229 Danish individuals present in electronic medical records, individuals who tested positive for COVID-19 had over three times the risk of death within 30-days of testing when compared to those who tested positive for influenza before the outbreak (5). They also had over three times the risk of ischemic stroke, two-times the risk of nephropathy, and over 1.5-times the risk of diabetes.
* A retrospective cohort study found that 1,916 adult patients with emergency department visits or hospitalizations with COVID-19 at 2 academic hospitals in New York City from 4 March 2020 through 2 May 2020 had 7.6 times (95% CI: 2.3-25.2) the odds of acute ischemic stroke when compared to 1,486 patients with ED visits or hospitalizations with influenza from 1 January 2016 to 31 May 2018 (6). The weakest association was found in a sensitivity analysis that excluded patients with emergency department treat-and-release visits (OR= 4.0; 95%CI: 1.2-13.7).
* Using US-based insurance-claims data, rates of CVD outcomes among 417,975 COVID-19 patients (median age 57 years old, diagnosed between April 1, 2020 and October 31, 2020) were compared to rates of events in 345,934 influenza patients (median age 47 years old, diagnosed between October 1, 2018 and April 31, 2019) (7). COVID-19 patients had higher venous thromboembolic (HR = 1.53, 95% CI: 1.38 to 1.70), DVT (HR = 1.36, 95% CI 1.19 to 1.56), and PE risk (HR = 1.82, 95% CI 1.57 to 2.10). There was no association arterial thromboembolic risk, except in patients without prior CVD (HR = 1.46, 95% CI: 1.25 to 1.71).
* When 3,948 hospitalized patients with COVID-19 (1 March to 31 May 2020) were compared with 5,453 historically hospitalized patients with influenza (1 October 2018 to 1 February 2020) in the national Veterans Health Administration electronic health record system, COVID-19 was statistically significantly associated with pulmonary embolism and deep vein thrombosis and showed marginal significance with cardiogenic shock and acute myocarditis when compared to those with influenza infection (8).
* Among 13,217 hospitalized patients with influenza and 579 hospitalized patients with COVID- 19 from the Statistics Netherlands cohort, the 30-day incidence of thrombotic complications in hospitalized patients with influenza (11%; 95% CI: 9.4 to 12) was lower than in hospitalized patients with COVID- 19 (25%; 95% CI: 18 to 32) (9). However, patients with influenza were much more likely to be diagnosed with arterial thrombotic complications alone (23%; 95% CI: 16 to 29) than patients with COVID-19 (4.4%; 95% CI: 1.9 to 8.8). Thus, it is unclear whether the pathogenesis is the same for arterial and venous thrombotic and the involvement of COVID-19 versus influenza in this process.
* A case-crossover study found that 1.5% of 36,975 California residents hospitalised with ischemic stroke had influenza in the previous year and the odds were higher in those with influenza within 15 days of their hospitalisation for stroke (OR = 2.88; 95% CI: 1.86 to 4.47 after adjusting for seasonal prevalence of influenza) and lowest when hospitalisation was within one year (OR = 1.50; 95% CI: 1.31 to 1.71) (10).
* A case-control study found that cases admitted with stroke had a 50% reduction in odds of having an influenza vaccination in that year (11). The conclusion summarises that “influenza vaccination may protect against brain infarction by reducing infections or may identify a subgroup of patients at low risk for stroke because of a better lifestyle.”

**GAP IN KNOWLEDGE**

* Existing studies were either unable to include a large number of covariates or did not have nationwide hospital data (4). Thus many studies were unable to determine the potential role of confounding factors in the association between COVID-19 and CVD events (5) and give precise estimates in representative samples, especially for particular patient subgroups (6, 8), regions, and time periods.
* Several studies had poor generalisability due to a limited patient setting or a limited number of years available to capture historical controls (6, 8). Certain flu seasons presented with worse predominant influenza subtypes and increased case-fatality rates than other years and so having a limited time period for historical data also restricts the severity of influenza present in the control group.
* Studies have also not adjusted for individuals receiving influenza vaccine even though influenza vaccination has been shown to be associated with a lower risk of stroke and myocardial infarction (12).
* Several studies have looked at a short-term incidence of CVD events, sometimes occurring within one month. Limiting follow-up time makes it difficult to determine whether the persistence of an association between infection and CVD events varies by the type of infection or event. It is still unclear how long patients with COVID-19 are at risk for CVD outcomes, how the persistence of an association varies by outcome type, and how all of this compares to patients infected with influenza.
* Some studies have indicated that they included CVD events that occurred during initial hospitalisation for COVID-19, however, patients with underlying cardiovascular disease may be more likely to have severe respiratory symptoms from COVID-19. Longer-term studies are needed, and tPEDWe studies need to exclude CVD events that occurred during the initial diagnosis of COVID-19. Studies have typically not stratified the analysis by prior history of stroke or myocardial infarction even though infection may trigger CVD more or less rapidly in those with previous CVD.
* Many of the published studies were based on studying subsequent risk in patients admitted with severe COVID-19 infection. Therefore, little is known about whether the magnitude of subsequent risk varies according to whether patients are hospitalised or not hospitalised.

**STUDY DESIGN**

A population-based cohort study using linked electronic health records.

**RESEARCH QUESTIONS**

1. What is the risk of first fatal or non-fatal ischaemic stroke, MI (‘arterial), cerebral sinus thrombosis, mesenteric or portal vein thrombosis, PE, DVT (‘venous thromboembolism’) in patients who test +ve for SARS-CoV2 (COVID+) compared with uninfected patients and how does this compare with people with viral influenza or pneumonia (non-COVID+) infection prior to the coronavirus epidemic?
2. Does the effect of COVID+ infection on outcomes persist longer term than that of non-COVID+ infection?
3. Does the magnitude of subsequent risk vary according to whether patients are hospitalised or not hospitalised due to their infection?

**SOURCE POPULATION**

1. **COVID infection analysis**

**Exposure group:**

Everyone with a positive PCR test, hospital admission, intensive care admission, or primary care/GP record of COVID taking the first diagnosis of COVID-19 from any source (primary and seconday care) from 1st January 2020 to 31st December 2021.

* +ve PCR test in PATD (COVID PCR test data); or
* Primary care COVID-19 diagnosis in WLGP; or
* Hospital admission in PEDW with the ICD10 code U07.1;
* Confirmed COVID-19 case in intensive care data (ICNC).

Any COVID exposure with hospitalisation:

* Hospital admission with COVID in primary positionand
* Hospital admission within first 28-days of COVID

Any COVID exposure without hospitalisation

* COVID and no hospitalisation within 28 days

**Comparison group:**

Everyone without a COVID diagnosis, a viral influenza infection, nor a viral/bacterial pneumonia infection from any source (primary and seconday care) from 1st January 2020 to 31st December 2021.

1. **non-COVID+ infection analysis**

**Exposure group:**

Everyone with a positive PCR test, hospital admission, intensive care admission, or primary care/GP consultation with a viral influenza infection or viral or bacterial pneumonia from 1 January 2016 to 31 December 2019 from any source (primary and seconday care).

* +ve PCR test in WRRS; or
* Primary care diagnosis in WLGP; or
* Hospital admission in PEDW with the relevant ICD10 codes;
* Confirmed viral influenza or viral/bacterial pneumonia case in intensive care data (ICNC).

Any non-COVID+ infection with hospitalisation:

* Hospital admission with viral influenza or viral/bacterial pneumonia in primary position, and
* Hospital admission within first 28-days of influenza or viral/bacterial pneumonia

Any non-COVID+ exposure without hospitalisation

* Influenza or viral/bacterial pneumonia and no hospitalisation within 28-days

**Comparison group:**

Everyone without a viral influenza infection, nor a viral/bacterial pneumonia infection from 1 January 2016 to 31 December 2019 (primary and seconday care).

**INCLUSION CRITERIA**

* have a record in the primary care extract;
* alive on 1st January 2020 for COVID+ analysis;
* alive on 1st January 2016 for the non-COVID+ infection analysis;
* patients have mandatory fields completed: sex, week of birth, Anonymised Linkage Field (ALF, a unique anonymised encrypted person/patient identifier).

**EXCLUSION CRITERIA**

* any patients/records where a COVID-19 infection is recorded prior to 1st January 2020;
* linkage is not possible;

QA criteria

* Year of birth is
  + before the date that NHS was established (5th July 1948);
  + after the year of death;
  + after the current date (impossible date in the future);
  + after the event date;
  + <18 years of age on the index date
* The date of death is
  + before index date;
  + before the date of the event;
  + past the current date (impossible date in the future) or end of the study period.

**DATA SOURCES**

**Wales (SAIL)**

* COVID C20 (all people alive and resident in Wales from 01/01/20) and C16 (counterfactual from 01/01/16 to end 2019) total population cohorts 3.2M. Censored by migration out of Wales and death.
* Patient Episode Database for Wales (PEDW).
* Consolidated mortality with 4 separate mortality data sources (Welsh Demographic Service Dataset (WDSD) – population spine weekly flows, ONS - monthly and daily flows (ADDE and ADDD), and records from the MPI (Master Patient Index) - daily flows (CDDS)).
* Pathology data COVID-19 test results (PATD) daily flows from NHS and Public Health Wales (PHW) laboratories and Lighthouse laboratories, including antigen and antibody testing - Pillar 1 and 2.
* Primary care data (WLGP), available on 86% that provide data to SAIL on a monthly basis containing all diagnostic, referral, prescribed medication.
* Pathology data COVID-19 test results (PATD) daily flows from NHS and Public Health Wales (PHW) laboratories and Lighthouse laboratories.Wales Results Reporting Service (WRRS)
* Community pharmacy dispensing (WDDS).
* Intensive Care National Audit & Research Centre (ICCD, ICNC).
* Emergency Department Data Set (EDDS)
* The Office for National Statistics (ONS) Census 2011 (CENW), pending approvals.

**TARGET POPULATION**

Conclusions will be made about the general patient population of Wales.

**COVARIATES**

POTENTIAL CONFOUNDERS defined on index date, with a look back in GP and hospital admission for each person:

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| * Sex | categorical, GP, where >1 sex recorded, excluded; |
| * Age | in years (continuous), at index date, |
| * Ethnicity | Categorical; ONS Census national ethnicity spine method |
| * Deprivation | continuous, most recent recorded prior to the index date. WIMD (Welsh Index of Multiple Deprivation) version 2019 |
| * Medications | medication within 3 months prior to index date for COVID infection analysis. |
| * Number of disorders | Number of disorders recorded in WLGP within 3 months prior to index date, using Read codes used for Charlson comorbidity score. |
| * Smoking | current/ex-/never/unknown most recent prior to inception; GP. |
| * Any Surgery | yes/not recorded one-year prior to index date. |
| * Hypertension or antihypertensive medication | yes/not recorded from the start of record to the index date, using PEDW, WLGP, WDDS for COVID infection analysis; and PEDW, WLGP for non-COVID infection analysis. |
| * Elixhauser Comorbidity Index | Total continuous score. |
| * Co-infection | * co-infection of influenza, pneumonia, or another respiratory virus in COVID+ patients (two-week time window); * co-infection of another respiratory illness (other than viral influenza or viral/bacterial pneumonia) in non-COVID+ patients (two-week time window). |

History of the following diseases (yes/no recorded from the start of record to index date)

* Diabetes
* Depression
* Obesity
* Cancer
* COPD
* CKD
* Liver disease
* Dementia
* Any CVD

Dispensing

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| * BP-lowering | yes/no/unknown; BNF chapter 2.5 at least one prescription within 3 months prior to inception in dispensing data for COVID infection analysis; and related Read codes in WLGP 3 months prior to inception for non-COVID infection analysis. |
| * Lipid-lowering | yes/no/unknown; BNF chapter 2.12 at least one prescription within 3 months prior to inception in dispensing data for COVID infection analysis; and related Read codes in WLGP 3 months prior to inception for non-COVID infection analysis. |
| * Anticoagulant/antiplatelet | yes/no/unknown; BNF chapter 2.8.2 at least one prescription within 3 months prior to inception in dispensing data for COVID infection analysis; and related Read codes in WLGP 3 months prior to inception for non-COVID infection analysis. |

**SUBGROUP ANALYSES (only if there are sufficient numbers of events)**

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| Age | Categorised into groups |
| Sex | categorical |
| Previous CVD | yes/not known history of myocardial infarction, angina, any stroke or heart failure. |
| Antiplatelet/anticoagulant use | yes/no/unknown (unknown if patient’s GP practice not in prescription extract); BNF chapter 2.9 at least one prescription within 3 months prior to inception in dispensing data for COVID infection analysis; and related Read codes in WLGP 3 months prior to inception for non-COVID infection analysis. |

**OUTCOMES**

Each outcome is defined as the first event of that type following the start of follow-up in one of the following data sources: secondary care, primary care, or ONS death registry. For the primary analyses, we will use events in the primary position recorded in PEDW or death records. For sensitivity analyses of the main results, we will include events in any position. The relevant codes will be confirmed to be available or not from the primary care extracts in SAIL and, if required, will only be ascertained in PEDW or death records.

Events will be defined as fatal if they are followed by death of any cause within 28-days, or are only recorded as fatal (i.e. reported only in death records). We will examine all events and fatal events in separate analyses.

Lower limb fractures are included as an outcome that is unlikely to be affected by an infection.

**Composite events:**

* **Arterial events:** first of ischaemic stroke or stroke of unknown type or retinal infarction or myocardial infarction or another arterial thrombosis;
* **Venous events:** first of pulmonary embolism or lower limb deep venous thrombosis or intracranial venous thrombosis or intracranial venous thrombosis during pregnancy or portal vein thrombus or another deep vein thrombosis;
* **Deep vein thrombosis events**: first of DVT or DVT during pregnancy

**Individual events of different types**

**Arterial**

* Incident myocardial infarction in WLGP, PEDW or mortality data;
* Incident ischaemic stroke or stroke of unknown type or retinal infarction or spinal stroke in WLGP, PEDW or mortality data;
* Incident non-stroke non-MI arterial embolism in WLGP, PEDW or mortality data.

**Venous**

* Pulmonary embolism in PEDW or mortality data;
* Deep vein thrombosis in PEDW or mortality data;

***Ungrouped event types***

* Heart failure in PEDW or mortality data;
* Lower limb fracture in PEDW or ONS death;
* Haemorrhagic stroke in PEDW or ONS death

Date of onset defined as: date of start of PEDW or hospital admission spell with the event; OR date of General Practitioner (GP) consultation with the event; OR death with the event (whichever comes first).

**FOLLOW-UP FOR SURVIVAL METHODS**

The index date will be the time of the first infection of either a

* 1st January 2020 for the COVID+ analysis.
* 1st January 2016 for non-COVID+ analysis.

The cohort study will be censored at the first of:

* death;
* event of interest;
* patient moves and registers to a non-SAIL GP and WLGP data no longer becomes available;
* 31st December 2021 for COVID+ exposure analysis (or latest date possible);
* 31st December 2019 for non-COVID+ infection analysis.

**PRINCIPAL ANALYSES**

We will examine the distribution of baseline characteristics at index date in COVID+, non-COVID+ infection, and the comparison group for each analysis. For the primary analysis, we will compare the incidence rate of our outcomes after either COVID+ or non-COVID+ infection infection to that of the relevant comparison group using separate Cox regression models. Models will be run within subgroups to identify potential effect modification. We will split follow-up time into time periods since exposure, but the periods will be collapsed whenever there are too few events. We will tabulate numbers of outcome events, person-years of follow-up, and rates of events with time since exposure. Potential confounding factors (factors that predict both exposure and outcome, listed below) will be based on data recorded on or before the start of follow-up in each analysis. We will estimate (i) age and sex adjusted and (ii) fully adjusted HRs (when there are sufficiently many outcome events). The following risk factors for arterial and venous thrombotic events will be included as confounders: patient demographics including smoking status, deprivation, rural or urban setting, care home attendance, Elixhauser comorbidity index, medications, and past medical history of disease. . Variables selected in any model will be adjusted for in all models. The same selected variables will be adjusted for in models for all outcomes.

**Missing data**

All analyses will be “complete-case” analyses (note that many potential confounders are defined using the presence versus absence of specific codes in the EHRs, so have no missing values). We will not use multiple imputation or indicators for missing data.

Sensitivity analyses:

* + Exclude patients where outcome and diagnosis are during the same hospital admission because the ordering of infection and event is difficult to disentangle.
  + Examine flu and pneumonia infection alone.
  + Including and excluding day 0 estimates (i.e. influenced by reverse causality).

**LIMITATIONS**

* Testing for COVID-19 may have been more comprehensive in 2020 than influenza/pneumonia testing was in previous years.
* Codes change over time and if the codes, or their use by healthcare workers, are different for historical flu cases and COVID+ cases then the results may be biased. Also, care and diagnostic tools may have changed from when historical controls were presented to healthcare to when COVID+ patients did later on in 2020.
* Patients with certain risk factors related to CVD may be more or less susceptible to COVID versus influenza or pneumonia.
* Availability of potential confounders may vary by country due to differences in the availability of linked datasets and variables contained in them. A meta-analysis across the countries of the UK may reflect country-specific effect estimates that are adjusted for different covariates.

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