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Kidney injury following Covid-19

- a whole population approach

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Academic dissertation

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Abstract

Background
Coronavirus disease 2019 (Covid-19) was initially considered a respiratory disease but was soon recognised as a multi-organ disease, including the kidneys. Previous research on Covid-19-associated kidney injury has been conducted in limited cohorts, leaving questions about the impact at the population level as well as on the kidney structure.

Overall Aim: To determine the extent of kidney injury following Covid-19, whether disease severity modified the risk, and whether novel kidney injury biomarkers could be used as more sensitive indicators of kidney injury.

Material and Methods
In Studies I-II and IV, whole-population Swedish data from 2020 to 2022/2025 were used. In Study III, whole-population Danish data from 2012 to 2022 were analysed. In Study V, data from a multicentre prospective cohort study in Sweden 2020-2021, including 141 mild and 77 moderate-to-severe Covid-19 patients, were used.

In Study I, data from the Swedish Intensive Care Register (SIR) were used as the reference to calculate the sensitivity and positive predictive values of procedure codes for intensive care (IC), mechanical ventilation (MV), extracorporeal membrane oxygenation (ECMO) and Covid-19 diagnosis registration in the Inpatient Register (IPR).

To create a harmonised severity index based on the registry format, the World Health Organisation (WHO) Clinical Progression Scale was translated into a severity index in Study II. A SARS-CoV-2 positive test was defined as exposure, and all-cause mortality 90 days after the initial 30 days of infection was defined as the outcome. Cox proportional hazards regression was used to assess whether disease severity was associated with mortality in Covid-19 patients compared with the background population.
To assess the reliability of ICD codes for kidney injury in the whole-population register data,

Study III validated ICD codes against laboratory-verified severe kidney injury. Sensitivity analysis with 95% confidence intervals and logistic regression, both adjusted and unadjusted, were performed to assess sensitivity.

The impact of Covid-19 severity on risk of kidney injury was determined using the self-controlled case series (SCCS) and Cox regression method in Study IV. The SCCS method was utilised to determine the duration at risk of kidney injury, and a whole-population approach using Cox regression was applied to determine the risk of kidney injury compared to the background population.

Since creatinine is a poor marker for identifying early stages of kidney injury, glomerular and tubular kidney injury biomarkers were quantified in plasma samples in Study V. Mann-Whitney U tests, Spearman's correlations, and linear mixed models were applied to evaluate differences in kidney injury biomarkers between mild and moderate-to-severe Covid-19 patients.

Results
In Study I, the sensitivity of a code in the Swedish IPR, compared with the SIR, was 39.7% (IC), 78.2% (MV), and 100% (ECMO), respectively. Variation in data completeness was observed across healthcare regions. Through Study II, the WHO Covid-19 clinical guidelines were translated into ten categories, reflecting the increasing need for health care interventions. Higher age and comorbidity burden were associated with mortality following Covid-19. After the initial 30 days (the time to define the highest disease severity), 90-day all-cause mortality increased with disease severity.

In Study III, a mismatch was observed between laboratory-verified severe kidney injury and diagnosed kidney injury, with an unadjusted sensitivity of 47.3%. Underdiagnosis was more common among men and people aged >80 years. In Study IV, the risk of kidney injury following Covid-19, evaluated with the incidence rate ratio, was increased up to 60 days. The risk was higher in men, increased with higher disease severity, and highest in the 51-74 age group. In Study V, we identified differences in tubular injury biomarkers between patients with moderate/severe and those with mild Covid-19, indicating that hospitalised patients were more affected up to 6 months post-infection.

Conclusions
These studies show an increased risk of kidney injury associated with Covid-19. The results highlight the importance of vaccination to prevent severe disease, as well as follow-up to detect kidney injury and to prevent deterioration. These studies also emphasise the importance of national health registers, combined with standardised definitions and reporting, for kidney injury, medical interventions, and Covid-19 disease severity.

Keywords: Covid-19, kidney injury, disease severity, biomarker, epidemiology

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