Impact of COVID-19 Severity on Long-term Events in US Veterans using the Veterans Affairs Severity Index for COVID-19 (VASIC)

Running Title: COVID-19 Severity and Long-term Events

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Abstract

In this retrospective cohort study of 94,595 SARS-CoV-2 positive cases, we developed and validated an algorithm to assess the association between COVID-19 severity and long-term complications (stroke, myocardial infarction, pulmonary embolism/deep vein thrombosis, heart failure, and mortality). COVID-19 severity was associated with a greater risk of experiencing a long-term complication days 31-120 post-infection. Most incident events occurred days 31-60 post-infection and diminished after day 91, except heart failure for severe patients and death for moderate patients, which peaked days 91-120. Understanding the differential impact of COVID-19 severity on long-term events provide insight into possible intervention modalities and critical prevention strategies.

Key Words

COVID-19, SARS-CoV2, Veterans, Epidemiology, electronic health records (EHR)

Background

Research has shown that adults infected with SARS-CoV-2 experience increased healthcare utilization, cardiovascular complications, and greater risks of death, especially within the first 30 days following infection[1-5]. Short-term risks (<30 days) for COVID-19 related cardiovascular events have been well-documented, but evidence is still emerging on long-term risks (>30 days)[3]. Understanding long-term clinical outcomes is especially critical when assessing COVID-19 prognosis in Veterans, who have higher rates of cardiovascular disease compared to the general US population [6]. Furthermore, quantification of COVID-19 severity and their impact on long-term events provides new insight into clinical care and management.

The Clinical Progression Scale for COVID-19 (graded 1 to 10: uninfected to death) was developed by the World Health Organization (WHO) to classify and standardize severity of COVID-19 disease[7]. While correct identification of COVID-19 severity is critical in understanding prognosis of the disease, the granularity of data required to correctly classify patients into the 10-point scale makes it difficult for most clinicians or researchers to accurately use. Utilizing national electronic health record (EHR) data from the Veterans Health Administration (VHA), we developed an adaptation of the WHO scale to create a four-category VA Severity Index for COVID-19 (VASIC). VASIC was validated and applied to a nationwide sample of SARS-CoV-2 positive Veterans' data to assess the association of VASIC severity and long-term complications (stroke, myocardial infarction (MI), pulmonary embolism (PE)/deep vein thrombosis (DVT), heart failure (HF), and mortality). VASIC can be readily applied to EHR data to quantify COVID-19 disease severity and enables the standardization of clinical decision-making for 30-day survivors.

Methods

We used VHA EHR data and Medicare and Medicaid services (CMS) data to create a national sample of Veterans ≥18 years of age who were both classified as a confirmed positive case by the VA National Surveillance Tool (NST), and had a positive SARS-CoV-2 PCR lab result within the VHA between March 1, 2020- December 31, 2020[8]. Infection date was defined as the first positive PCR

result in the VA. Cases were classified according to the highest VASIC status experienced by day 30 post-infection, and long-term complications were assessed days 31- 120 post-infection. For comparison, we included a control group consisting of patients with a negative SARS-CoV-2 PCR test, who were admitted with pneumonia diagnosis within the same timeframe as the cases.

The VASIC algorithm, was created by summarizing the 10-point WHO Scale into 4 categories: mild (WHO scores 1-3), moderate (4-5), severe (6-9), and most severe (10)[7]. All VASIC categories required the same definition - a positive PCR and satisfied of one of the following criteria: mild (not hospitalized or hospitalized for ≤24 hours); moderate (hospitalized for > 24 hours, with or without low flow oxygen therapy); severe (hospitalized for > 24 hours with high flow oxygen therapy, intubation, mechanical ventilation, vasopressors, Endothelial Corporeal Membrane Oxygenation (ECMO) or kidney dialysis); and most severe (dead). Data for all categories was ascertained from EHR procedure codes between days 0-30 post-infection. COVID-19 related hospitalizations were attributed to patients who were hospitalized -7 days to +30 days relative to the date of their first positive PCR test.

To validate the VASIC algorithm, an extensive review of VHA clinical notes was performed for a random sample of 200 patients. Adjudication was conducted by three clinical subject matter experts, and each patient record was examined by at least two reviewers. Consistency across reviewers was analyzed using Cohen's Kappa statistic. The validated algorithm was retrained using the gold-standard labels and applied to 94,595 SARS-CoV-2 positive Veterans at day 30 post-infection.

Long-term complications were assessed up to day 120 post-infection, or until their date of death. New and decompensated events were assessed at 3 different time points post-infection: 1) 31-60 days, 2) 61-90 days 3) 91-120 days. Major events evaluated included stroke, MI, PE/DVT, HF, and mortality, which were identified by the occurrence of one inpatient or two outpatient ICD codes. To improve classification of incident and recurrent events, a 5-year history of stroke, MI, PE/DVT, HF was ascertained prior to the infection date. Poisson regression was used to test the longitudinal effects of COVID-19 severity on monthly incidence rates, with a separate model for each event.

This study was reviewed and approved by the institutional review boards of Emory University (IRB# 389) and VA Boston Healthcare System (IRB# 3310-X). This study was restricted to secondary data analysis, and thus, the requirement for informed consent from participants was waived. This manuscript follows the
Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Results

Among the 94,595 SARS-CoV-2 positive Veterans, VASIC classified 72,253 as mild, 13,815 moderate, and 4,394 severe, and identified 4,133 most severe. The median age of those infected was 60 years, with 87% male, 63.2% White, and 24.4% Black (Supplementary Table 1). The interrater reliability of the VASIC algorithm, as measured by Kappa statistic, showed high concordance (0.83) and resulted in the following metrics across the three categories: mild vs others (PPV: 0.86, Sensitivity:0.73, Specificity 0.92); moderate vs others (PPV: 0.92 Sensitivity: 0.87, Specificity: 0.84); and severe vs others (PPV:0.67, Sensitivity: 0.97, Specificity 0.92)[9]. VASIC classified approximately 10% of patients as moderate who had clinically mild symptoms but were hospitalized for >24 hours due to reasons unrelated to COVID-19.

A summary of incident events by VASIC category is shown in Table 1. The incident rates for complications by VASIC (mild, moderate and severe, respectively) from day 31-120 were: stroke (0.2%, 0.7%, and 1.1%); MI (0.2%, 0.7%, 1.0%); PE/DVT (0.2%,0.6%,1.5%); HF (0.2%, 1.1%, 2.1%); death (0.6%, 5.2%,9.4%). Severe patients had the highest rates of incident events, followed by moderate then mild. While the risks of incident events decrease for moderate and severe patients beyond day 30, risks for those in the mild category increase. Compared to the control group, severe patients had statistically higher rates across all events within the first 30 days of SARS-CoV-2 positive test. Within the 31 to 120 days after SARS-CoV-2 positive test, higher rates were observed for incidence of PE/DVT and death among those with VASIC-severe status compared to the control group. Deaths (n, (%)) among those who had a stroke, MI, PE/DVT, or HF within 31-120 days were

17 (7.00%), 19 (8.30%), 21 (8.20%), and 41 (12.06%), respectively. Demographics of Veterans who experienced incident events can be found in Supplementary Table 2.

Figure 1 and Supplementary Figure 1 show the incidence rate for each event per 1000 persons by week, post-infection. Among VASIC-mild patients, incidence of heart failure and stroke was significantly greater at 31-60 days compared to the first 30 days (p-values = 0.01 and 0.03, respectively). For most events and severity levels, incidence peaked in the first month post-infection (days 31-60) and then decreased over the course of follow-up. The decreasing trend in monthly incidence was significant for mortality (p-values = 2.8×10^{-12}, 0.001 , 5.8×10^{-35} for mild, moderate, and severe categories, respectively) and PE/DVT (p-values = 7.7×10^{-6}, 3.2×10^{-8}, 3.1×10^{-7}), but only significant for HF with moderate (p-value = 5.6×10^{-4}) and stroke with mild (p-value = 1.1×10^{-4}) and severe (p-value = 0.007).

Distributions of the baseline population that experienced any events during days 31-120 are shown by week in Supplementary Figure 2. Most complications were experienced within the first 3 weeks of follow up with the highest distribution of events occurring during week 1 of follow up across all VASIC categories. The highest percentage of death during follow up occurred among severe patients, 9.4%. The median lengths of hospitalization for the moderate and severe patients were 5 days (IQR=8) and 15 days (IQR=20), respectively.

Discussion

The VASIC algorithm was developed and validated on the largest single national EHR database to examine long-term outcomes of COVID-19. It can be applied to other EHR databases for which SARS-CoV-2 PCR lab tests are available. Our results illustrate that patients experience long-term complications beyond 4 weeks post-infection, and that incidence of these events increase by COVID-19 disease severity. The importance of clinical monitoring for COVID-19 patients well beyond their initial infection stage is highlighted, as the risks of poor cardiovascular events and death remain elevated after 30 days and increase beyond day 30 for mild patients.

Acute clinical manifestations of COVID-19 have been well documented, however, evidence is still emerging on the complexities of long-term complications of COVID-19. While current literature supports our evidence that the risk of incident events extends well beyond 30 days post-infection, until now there has not been a validated method to assess these events by COVID-19 disease severity[10]. Our findings highlight the importance of understanding the clinical prognosis of patients exhibiting various severities of COVID-19, and the ways in which this can enable individualized clinical care. VASIC can be incorporated into genetic studies and EHR trial emulation analyses, using severity status as an endpoint to identify novel treatments against COVID-19, and to evaluate efficacy and safety of COVID-19 vaccines. Delineating cases that present as clinically mild/asymptomatic but are hospitalized for concerns unrelated to COVID-19 continues to be a challenge for EHR algorithms. Future work will also include further examination of factors that contribute to a patient's prognosis such as biomarkers of severe disease and continued investigation of progression of COVID-19.

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Conflict of interest

The authors declare no conflicts of interest related to this research.

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study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Author contributions

Study design was conceived by AG, YP, TC, PWFW, AMH and KC. Validation methods were conceived by KC, TC, and YLH. Chart reviews and algorithm validation were conducted by VT, XTN, and MM. Expert clinical considerations and insight were provided by SL, PST, JMG, PWFW, and AHM. Data collection and organization were performed by YLH, KC, YP, HG, and DP. Funding and resources were acquired by SM, JMG, SW, JPC, PT, PWFW, and KC. Project administration and supervision was done by SM, JMG, JPC, PT, SW and KC. Analyses were performed by ATD, YLH, KC, YP, HG, DP and DRG. All authors participated in interpreting results, manuscript writing and critical revision; all authors approve of the manuscript submission in its current form. AG and KC are the guarantors of the manuscript, including study design, analyses, and drafting, submission, and publication of the manuscript.

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Figure Legend

Figure 1. Incident rates per 1,000 person for all events 31-120 days post SARS-CoV-2 infection.

Incident rates are shown for stroke, myocardial infarction, pulmonary embolism/deep vein thrombosis, and heart failure. Events are broken down by severity category for days 31-60, 61-90, and 91-120. a: includes ischemic, hemorrhage and transient ischemic strokes

Supplementary Figure 1. Incident rates per 1,000 persons for mortality 31-120 days post SARS-CoV-2 infection.

Incident rates are shown for mortality. Events are broken down by severity category for days 31-60, 61-90, and 91-120.

Supplementary Figure 2. Distribution of events by week for SARS-CoV-2 positive Veterans experiencing any event during follow-up.

Weekly distribution of events during the follow-up period. Week 1 starts on day 31 post-infection. a: includes ischemic, hemorrhage and transient ischemic strokes.

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Table 1. Incidence of MI, stroke, HF, DVT/PE or death for SARS-CoV-2 positive Veterans by VASIC categories

Table 1a. Key incident events within the first 30 days of SARS-CoV-2 positive test (N=94,595) by VASIC categories

Events	**VASIC-Mild** (n= 72,253)	**VASIC-Moderate** (n=13,815)	**VASIC-Severe** (n=4,394)	**VASIC-Most Severe** (n=4,133)	**Negative Control*** (n=2,158)	**Moderate vs Control** (*p*-value)	**Severe vs Control** (*p*-value)
Stroke[a], No. (%)	47 (0.07)	386 (2.79)	171 (3.89)	146 (3.53)	53 (2.33)	0.20	0.001
MI, No. (%)	37 (0.05)	488 (3.53)	291 (6.62)	349 (8.44)	88 (3.86)	0.43	<0.0001
PE/DVT, No. (%)	65 (0.09)	445 (3.22)	352 (8.01)	209 (5.06)	58 (2.55)	0.86	<0.0001
HF, No. (%)	34 (0.05)	498 (3.60)	287 (6.53)	219 (5.30)	195 (8.56)	<0.0001	0.002

Table 1b. Key incident events between day 31 to 120 days after SARS-CoV-2 positive test (N=90,462) among those in VASIC-mild, moderate, and severe categories

Events	**VASIC-Mild** (n= 72,253)	**VASIC-Moderate** (n=13,815)	**VASIC-Severe** (n=4,394)	**Negative Control*** (n=2,158)	**Moderate vs Control** (*p*-value)	**Severe vs Control** (*p*-value)
Stroke[a], No. (%)	134 (0.2)	72 (0.52)	37 (0.84)	10 (0.46)	0.73	0.09
MI, No. (%)	112 (0.16)	79 (0.57)	38 (0.86)	16 (0.74)	0.34	0.60

PE/DVT, No. (%)	126 (0.18)	74 (0.53)	56 (1.27)	15 (0.69)	0.36	0.03
HF, No. (%)	151 (0.22)	123 (0.89)	66 (1.50)	31 (1.44)	0.02	0.84
Death, No, (%)	403 (0.56)	725 (5.25)	415 (9.44)	128 (5.93)	0.19	<0.0001

Abbreviations: MI, myocardial infarction; PE, pulmonary embolism; DVT, deep vein thrombosis; HF, heart failure; VASIC, VA Severity Index for COVID-19
VASIC category definitions: VASIC-Mild: non-hospitalized/ hospitalized ≤24 hrs; VASIC-Moderate: hospitalized for > 24 hrs; VASIC-Severe: hospitalized for >24hrs with high flow oxygen, intubation, mechanical ventilation, vasopressors, ECMO or kidney dialysis; VASIC-Most Severe: dead
a: Includes ischemic, hemorrhage and transient ischemic strokes
*Those with negative SARS-CoV-2 test, whose primary hospitalization diagnosis was pneumonia

Figure 1

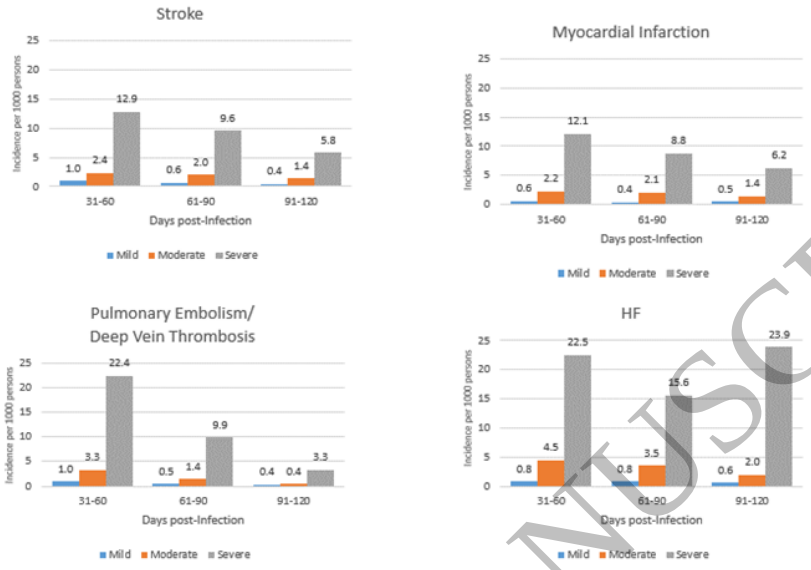

Figure 1
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