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Evolution of Care and Outcomes Across Surges in Hospitalized Patients with Coronavirus Disease 2019

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PII: S0002-9343(22)00672-6
DOI: https://doi.org/10.1016/j.amjmed.2022.08.035
Reference: AJM 16904

To appear in: *The American Journal of Medicine*

Received date: 8 July 2022
Accepted date: 26 August 2022

Please cite this article as: Patrick J O'Hayer , Alexi Vasbinder , Elizabeth Anderson , Tonimarie Catalan , Brayden Bitterman , Ibrahim Khaleel , Grace Erne , Annika Tekumulla , Caroline Tilley , Feriel Presswalla , Namratha Nelapudi , Jiazi Chen , Medha Tripathi , Matthew Rochlen , Loni Rambo , Noor Sulaiman , Pennelope Blakely , Yiyuan Huang , Lili Zhao , Rodica Pop-Busui , Salim S. Hayek , Evolution of Care and Outcomes Across Surges in Hospitalized Patients with Coronavirus Disease 2019, *The American Journal of Medicine* (2022), doi: https://doi.org/10.1016/j.amjmed.2022.08.035

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Clinical Research Study

Evolution of Care and Outcomes Across Surges in Hospitalized Patients with Coronavirus Disease 2019

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Clinical Significance

- The inpatient management of hospitalized patients with Covid-19 has markedly changed over time.
- Outcomes for hospitalized Covid-19 patients have dramatically improved.
- Inflammatory burden of Covid-19 has decreased over time.

- Binary logistic regression analysis indicates that hospitalization later in the pandemic is independently associated with improved survival, even after controlling for relevant patient and treatment factors.

ABSTRACT

Background: The coronavirus disease 2019 (Covid-19) pandemic has unfolded in distinct surges. Understanding how surges differ may reveal important insights into the evolution of the pandemic and improve patient care.

Methods: We leveraged the Michigan Medicine Covid-19 Cohort (M^2C^2), a prospective observational study at an academic tertiary medical center that systematically enrolled 2309 consecutive patients hospitalized for Covid-19, comprising five distinct surges.

Results: As the pandemic evolved, patients hospitalized for Covid-19 tended to have a lower burden of comorbidities and a lower inflammatory burden as measured by admission levels of C-reactive protein, ferritin, lactate dehydrogenase, and d-dimer. Use of hydroxychloroquine and azithromycin decreased dramatically after Surge 1, while use of corticosteroids and remdesivir markedly increased (P<0.001 for all). In-hospital mortality significantly decreased from 18.3% in Surge 1 to 5.3% in Surge 5 (P<0.001). The need for mechanical ventilation significantly decreased from 42.5% in Surge 1 to 7.0% in Surge 5 (P<0.001), while the need for renal replacement therapy (RRT) decreased from 14.4% in Surge 1 to 2.3% in Surge 5 (P<0.001). Differences in patient characteristics, treatments, and inflammatory markers accounted only partially for the differences in outcomes between surges.

Conclusions: The Covid-19 pandemic has evolved significantly with respect to hospitalized patient populations and therapeutic approaches, and clinical outcomes have dramatically

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improved. Hospitalization after the first surge was independently associated with improved outcomes, even after controlling for relevant clinical covariates.

KEY WORDS: *Covid-19, surge, outcomes, corticosteroids, dexamethasone, remdesivir, tocilizumab, hydroxychloroquine, azithromycin*

INTRODUCTION

The approach to caring for hospitalized patients with coronavirus disease 2019 (Covid-19) has evolved rapidly with the emergence of clinical trials debunking certain therapies such as hydroxychloroquine and establishing effective ones such as corticosteroids. Dexamethasone has been shown to significantly improve survival among Covid-19 patients with hypoxic respiratory failure, and remdesivir has been shown to decrease time to clinical recovery[1-5]. These therapies are now routinely administered to hospitalized patients with severe Covid-19. Conversely, therapies such as hydroxychloroquine and azithromycin, which were more commonly used early in the pandemic, have been found to be ineffective and in many cases harmful[6-9].

Fortunately, the mortality of patients hospitalized for Covid-19 has steadily decreased over the past two years[10]. Whether the improvement in survival is related to patient factors, therapeutic factors, or other factors remains unclear. Epidemiologic studies reporting on Covid-19-related outcomes which rely on automated electronic data extraction or billing codes are limited by the lack of granularity and the inability to differentiate between patients hospitalized specifically for Covid-19 and those only with a positive SARS-CoV-2 test[11]. To better understand the evolution of the Covid-19 pandemic and identify factors associated with improved survival, we leveraged the Michigan Medicine Covid-19 Cohort (M^2C^2), a prospective observational study which systematically enrolled patients hospitalized specifically for Covid-19. The systematic and prospective enrollment of patients in this cohort, and the availability of inflammatory biomarkers

measured on admission allow for the granular characterization and comparison of patients' characteristics, inflammatory burden, and outcomes across distinct Covid-19 surges.

METHODS

Study Design

The Michigan Medicine Covid-19 Cohort (M^2C^2) is an ongoing, single-center, prospective observational cohort study that includes all patients hospitalized at the University of Michigan Medical Center (Michigan Medicine) specifically for Covid-19 since the start of the pandemic[12-14]. Michigan Medicine is an academic medical center located in Ann Arbor, Michigan, USA and is a quaternary referral center serving patients across the state of Michigan and surrounding regions of the United States, with over 2.6 million clinic visits, 95,000 emergency department visits, and 46,000 hospitalizations in 2021 alone. Overall, 69,527 patients (inpatients and outpatients) were diagnosed with a SARS-CoV-2 infection at Michigan Medicine, of whom 55% were women and 73% White. All patients with a PCR-confirmed SARS-CoV-2 infection and who were admitted primarily for Covid-19 between March 9th, 2020 and January 29th, 2022 were included. Patients noted to be SARS-CoV-2-positive on admission but hospitalized for reasons unrelated to Covid-19 were excluded. Individual patient data was extracted by detailed manual chart review and entered into a REDCap database (Vanderbilt University, TN), including demographic data, past medical history/comorbidities, inflammatory biomarker data, treatments administered, and outcomes. DataDirect, a self-service tool to access objective data from electronic medical records, was also used to supplement manual chart review. Blood samples were collected within 48 hours of hospitalization for biomarker measurement. This study has been approved by the University of Michigan Institutional Review Board.

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Surge Definitions

Surge 1 was defined as all Covid-19 hospital admissions from March 9th, 2020 through June 14th, 2020. Surge 2 was defined as all Covid-19 hospital admissions from June 15th, 2020 through February 20th, 2021. Similarly, Surge 3 was defined as February 21st, 2021 through June 24th, 2021. Surge 4 was defined as June 25th, 2021 through December 18th, 2021. Surge 5 was defined as December 19th, 2021 through January 19th, 2022. These cutoff dates were chosen based on statewide Covid-19 transmission rates and daily hospitalizations for Covid-19 in Michigan, USA (**Figure 1**).

Patient Characteristics, Biomarkers, Therapies, and Outcomes

We examined five Covid-19 surges in terms of patient characteristics, inflammatory biomarkers, therapeutic approaches, and clinical outcomes. Biomarkers examined included C-reactive protein (CRP, mg/dl), ferritin (ng/ml), lactate dehydrogenase (LDH, International Units/L), and D-dimer (mg/L fibrinogen equivalent units), measured as previously described[12]. All biomarkers were measured as part of clinical care at the University of Michigan CLIA-approved central laboratory.

Treatments were considered as binary categorical variables (received/not received at any time during the course of hospitalization), and included hydroxychloroquine, azithromycin, tocilizumab, remdesivir, and corticosteroids. We did not include treatments received in the outpatient setting prior to admission.

Clinical outcomes were determined by manual chart review of primary provider documentation and included mortality, need for intensive care unit (ICU) admission, need for mechanical ventilation, need for renal replacement therapy (RRT), and hospital length-of-stay (LOS, days).

Statistical Analyses

Categorical variables were expressed as the number of patients (n) and the percentage of patients within each surge. Continuous variables were expressed as the mean and standard deviation or the median and interquartile range (IQR) for normally and non-normally distributed data, respectively. Baseline patient characteristics were evaluated for significant differences between surges using ANOVA (for normally distributed continuous variables) or a Chi-Square test (for categorical variables). Kruskal-Wallis testing was used to test for significant differences in inflammatory biomarkers across the five surges given non-normally distributed data. For visualization, we used radar plots to demonstrate differences in patient characteristics, treatments, outcomes, and inflammatory biomarkers (including a composite biomarker score) across the five surges. The composite biomarker score of a patient was calculated by the summation of the leave-one-out products of the ranks (of the patient) of each biomarker, which was a combined measurement of the patient's rank of biomarkers within the cohort[15]. The percentages and the median of the standardized values (which were calculated by subtracting the minima of the variable in the cohort from the original values and divided by the range of the variable) were produced for binary variables and continuous variables (inflammatory markers) respectively.

Surge and Inflammatory Markers

To assess whether the differences in levels of inflammatory markers across surges are related to differences in clinical characteristics, we performed multivariable linear regression modeling for each biomarker as well as the composite biomarker score (dependent variables), including Surge (reference group is Surge 1) in the model along with age, sex, race (white vs non-white), body

mass index (BMI), hypertension, diabetes mellitus, coronary artery disease, heart failure, and estimated glomerular filtration rate (eGFR) on admission.

Surge and Outcomes

For multivariable analysis we used binary logistic regression modeling to identify factors independently associated with in-hospital mortality, and the composite outcome of in-hospital mortality, need for mechanical ventilation, or need for renal replacement therapy (RRT). To identify the contribution of clinical characteristics, treatments, and inflammatory markers, a series of 4 models was used as follows, with the dependent variable for all models being in-hospital death. The analysis was then repeated with the composite outcome of death, need for mechanical ventilation, or need for renal replacement therapy (RRT) as the dependent variable. Model 0 included surge alone as a single independent variable, with separate analyses comparing surge 1 (reference) and all other surges. Model 1 included surge, age, sex, race (white vs non-white), body mass index (BMI), hypertension, diabetes mellitus, coronary artery disease, heart failure, and eGFR on admission. Model 2 included surge, the aforementioned clinical covariates, and the treatment variables remdesivir or corticosteroids. Finally, Model 3 included surge, the aforementioned clinical and treatment covariates, and the composite score of biomarkers of inflammation (previously defined). All analyses were performed using R Version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Patient Characteristics

Our study included a total of 2309 patients hospitalized with Covid-19 since the start of the pandemic, 515 admitted in Surge 1, 658 admitted in Surge 2, 442 admitted in Surge 3, 523 in Surge 4 and 171 in Surge 5. We found significant differences in the clinical characteristics of

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patients hospitalized during these distinct surges (**Table 1**). While the mean patient age decreased after the initial two surges (from 60.1 years for Surge 1 to 54.5 years for Surge 3), it increased again in Surge 5 (60.5 years for Surge 5). The proportion of women remained steady across the first 4 surges (range 41.6% to 44.2%) and increased in Surge 5 to 52.0%. Black patients made up a large proportion of patients in the initial Surge (46.4%), stabilized during Surges 2-4 (12.8%-17.9%), then rose again to 22.8% during Surge 5. Out of hospital transfers comprised 30.2% of patients in the initial surge, declining to <5% in surges 4 and 5 (**Table 1**). The prevalence of comorbidities hypertension, cardiovascular disease and chronic kidney disease declined over 50% as the pandemic progressed (**Table 1, Figure 2A**). Diabetes mellitus remained a common comorbidity throughout all the surges (range 25.1% to 43.5%), including Surge 5.

Treatments

Hydroxychloroquine and azithromycin were commonly used during the initial surge (40.6% and 35.5% of patients respectively). The use of hydroxychloroquine subsequently dropped to <2% of patients, while 10.5% to 21.1% of patients received azithromycin in subsequent surges (**Table 1, Figure 2B**). Conversely, use of remdesivir and corticosteroids increased dramatically, from 10.1% and 30.7% in Surge 1 to 73.1-80.4% and 66.7%-82.5% in Surges 2-5, respectively. We did note a decrease in the use of corticosteroids during Surge 5 from 79.3% to 66.7%. The use of tocilizumab varied significantly; with 21.7% of patients treated during the initial surge, only 2.0% during Surge 2, then 13.5% to 20.4% during Surges 3-5.

Biomarkers of Inflammation

We noted significant differences in levels of inflammatory biomarkers across surges. Levels of CRP, ferritin, LDH, and D-dimer were highest in Surge 1 and exhibited a decline across surges

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(**Table 1, Figure 2C**). In multivariable analyses, it was found that later surges (relative to surge 1) were associated with significantly lower levels of CRP, ferritin, and D-dimer, even after controlling for patient factors (**Table 2).** The composite biomarker score was significantly higher for surge 1 relative to all other surges even after controlling for patient factors (**Table 2**).

Outcomes across Surges

Outcomes were the worst in the initial surge, with 55.5% of patients requiring admission to the intensive care unit (ICU), 42.5% requiring mechanical ventilation, 14.4% requiring renal replacement therapy (RRT), and 18.3% dying while hospitalized. While we saw variation across surges, all outcomes significantly improved over time compared to Surge 1 (P<0.001, **Table 1, Figure 2D**). Notably, in-hospital mortality was 5.3%, need for mechanical ventilation 7.0% and need for RRT 2.3% during Surge 5. Hospital length of stay also decreased from a median of 10 days (interquartile range [IQR] of 20) in the initial surge to 4 days (IQR 6) during Surge 5. Interestingly, we did note a higher mortality rate during Surge 4 (11.1%) compared to Surges 3 and 5.

We then conducted a binary logistic regression analysis to determine whether individual surges were associated with reduced mortality relative to surge 1. In model 0 (surge as the lone independent variable), all subsequent surges were associated with reduced mortality relative to surge 1 (**Supplemental Table 1**). In model 1 (controlling for patient factors), surges 2 and 4 were no longer independently associated with improved survival relative to surge 1, however surges 3 and 5 remained independently associated with improved survival relative to surge 1 (**Supplemental Table 1**). In model 2 (controlling for patient factors and treatment with remdesivir/corticosteroids) and model 3 (controlling for patient factors, treatment with remdesivir/corticosteroids, and inflammatory biomarkers), all subsequent surges were

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independently associated with improved survival relative to surge 1 even after controlling for these covariates (**Figure 3A, Supplemental Table 1**). When using the composite outcome of in-hospital death, need for mechanical ventilation, or need for RRT as the dependent variable, all models demonstrated that all surges after surge 1 were independently associated with reduced risk of the composite outcome, even after controlling for the aforementioned covariates (**Figure 3B, Supplemental Table 2**). Of note, the significance of estimates was minimally impacted with adjusting for covariates, suggesting that unmeasured factors beyond clinical characteristics, therapies, or inflammatory biomarkers account for the improved outcomes between surges.

DISCUSSION

As the Covid-19 pandemic continues to unfold, the clinical approach to hospitalized patients with Covid-19 has changed significantly with the emergence of new data. However, the degree to which therapeutic approaches have evolved and their impact on clinical outcomes has remained largely unquantified. Furthermore, although it is well recognized that clinical outcomes have overall improved, factors associated with improved survival have not been clearly elucidated. Here we leveraged a prospective observational study which systematically included all patients admitted specifically for Covid-19 since the beginning of the pandemic, and compared patients' clinical characteristics, inflammatory biomarkers, treatments, and clinical outcomes across distinct surges. We also conducted binary logistic regression analysis to identify factors associated with improved survival. Our data together tell the story of the evolution of the pandemic from the early days in March of 2020 through January of 2022.

The initial Surge was distinct**;** characterized by a higher prevalence of comorbidities (diabetes, hypertension, and chronic kidney disease), higher inflammatory markers (CRP, ferritin, LDH, D-dimer) and worse outcomes (mortality, need for mechanical ventilation, need for RRT). The

higher proportion of Black patients is consistent with the fact that overall, the pandemic has certainly disproportionately affected minority communities[12,16]. We also observed clear shifts in therapeutic approaches over time. The use of hydroxychloroquine and azithromycin was relatively common in Surge 1, then decreased dramatically with the advent of high-quality data that did not show any benefit but rather a signal for harm. Conversely, after the initial surge, treatment with corticosteroids and remdesivir became the standard of care for all patients requiring supplemental oxygen based on high-quality clinical trials (**Table 1, Figure 2B**). The fluctuations in tocilizumab utilization over time reflect the evolution of expert opinion and data over time. Initially, tocilizumab was used in the absence of high-quality data based on the reasonable hypothesis that IL-6 blockade would blunt the cytokine storm responsible for the most severe complications of Covid-19 (21.7% of patients in Surge 1), but use decreased dramatically in Surge 2 (2.1% of patients) as multiple initial studies failed to demonstrate a clear benefit. However, with the advent of later meta-analyses showing a reduction in all-cause mortality, tocilizumab saw a resurgence in use, with 13.5%-20.4% of patients receiving tocilizumab in Surges 3-5 (**Table 1**, **Figure 2B**)[17-18].

Along with these significant changes in therapeutic approach, our data demonstrate that clinical outcomes have markedly improved since the initial surge of the pandemic, with dramatic reductions in mortality, ICU admission, need for mechanical ventilation, and need for renal replacement therapy (**Table 1**, **Figure 2D**). Our results are consistent with a recent study that also found significantly improved outcomes among critically-ill patients with Covid-19 despite relatively stable patient characteristics[10]. We noted an increase in mortality during surge 4 (11.1% compared to 5.4% in surge 3). Although it is impossible to derive firm conclusions from the available data, the increase in mortality seen in Surge 4 may be related to the waning of

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immunity provided by the initial vaccination series for SARS-CoV-2, given the timeline relative to the deployment of the vaccines in early 2021. Although the vaccines remain highly effective in decreasing the risk of severe disease and death, studies have indicated that immunity does begin to decline after approximately two months[19]. Fortunately, in-hospital mortality rates significantly declined again to 5.3% in surge 5, as Omicron became the dominant SARS-CoV-2 variant.

Finally, we found that hospitalization during Surge 1 was independently associated with worse outcomes; and this relationship persisted even after controlling for relevant patient characteristics and treatment variables (**Figure 3, Supplemental Table 1-2).** This observation may in part reflect the strain on many health systems during the initial surge as hospital and ICU capacity was often exceeded, necessitating emergent transfers to our institution – as we noted that 32% of patients during the first surge were out-of-hospital transfers, a proportion that gradually declined to <5% in the latest surges. However, this also likely reflects the knowledge and experience that providers gained over time that impacted daily management decisions in myriad ways beyond the discrete therapies studied. One significant change in strategic approach that is difficult to quantify is the change in threshold for intubation for critically-ill Covid-19 patients with hypoxic respiratory failure. In the initial surge, many patients were intubated once they were requiring more than 6 liters/minute of supplemental oxygen to avoid potential aerosolization of the virus associated with heated high-flow nasal cannula[19]. In our experience, as the pandemic progressed and as concerns about viral aerosolization from high flow nasal cannula were mitigated, the threshold for intubation significantly increased and many patients were managed successfully with high flow nasal cannula, in some cases averting intubation and its associated risks. It is likely that this "higher intubation threshold strategy" also has led to improved outcomes, though

additional randomized clinical trials would be needed to evaluate this issue more definitively, and there are reasonable physiologic arguments to be made on both sides. The fact that later surges were independently associated with improved survival even after controlling for patient and treatment variables may also reflect evolution of viral strains, as well as the protective effects of vaccination in the latter surges.

Our study has several strengths, notably the prospective and systematic collection of granular data on the hospital course of patients hospitalized specifically for Covid-19, and the measurement of biomarkers of inflammation from samples collected within 48 hours of admission. Although our sample size is large, the single center nature remains the main limitation, as practices in a quaternary care center such as the University of Michigan may not reflect that of other centers. Data on the specific variant for each patient or vaccination status was unfortunately not available. Lastly, behaviors related to clinical management beyond administration of therapies is difficult to capture and quantify, although they are likely to have a major impact on outcomes.

CONCLUSION

In summary, we conducted a prospective observational study that analyzed the patient populations, inflammatory biomarkers, treatments, and outcomes across five distinct surges of hospitalized patients with Covid-19. Our data, taken together, effectively tell the story of the evolution of the pandemic at our academic medical center for the first roughly 22 months of the pandemic. Outcomes have improved significantly, and although this is certainly in part due to the adoption of effective treatments, our data suggest that there are other unmeasured factors at play that have also led to improved outcomes.

Declaration of Competing Interest

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None of the authors have conflicts of interest to disclose. The authors have no conflicts of interest to disclose. All authors participated in the research and preparation of the manuscript.

Funding Sources

AV is supported by a NHLBI funded post-doctoral fellowship (T32HL007853). SSH is funded by NHLBI 1R01HL153384-01, NIDDK 1R01DK12801201A1, U01-DK119083-03S1, and the Frankel Cardiovascular Center COVID-19: Impact Research Ignitor (U-M G024231) award. RPB is supported by NIH/NIDDK-1-R01-DK-107956-01, NIH U01 DK119083, the Juvenile Diabetes Research Foundation 5-COE-2019-861-S-B, and by a Pilot and Feasibility Grant from the Michigan Diabetes Research Center (NIH Grant P30-DK020572).

Acknowledgements

The authors acknowledge the University of Michigan Medical School Research Data Warehouse and DataDirect for providing data aggregation, management, and distribution services in support of the research reported in this publication. The authors are grateful to the services of the Microbiome Core supported by U2CDK110768, especially Chris Blair; the Michigan Clinical Research Unit including Wrenn Woodard and Dexter Hobdy, and the University of Michigan Medical School Central Biorepository for providing biospecimen storage, management, and distribution services in support of the research reported in the publication.

We would like to acknowledge the following persons for contributing to data collection: Tariq Azam, Chelsea Meloche, Rafey Feroze, Kishan J. Padalia, Danny Perry, Abbas Bitar, Erinleigh Michaud and Peiyao Zhao.

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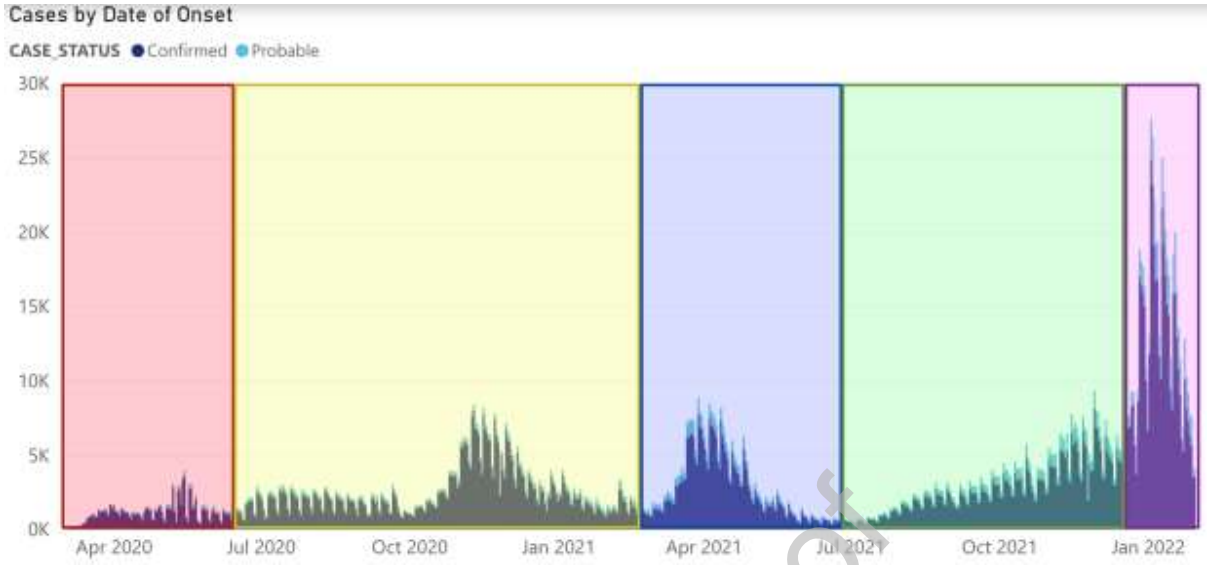

Figure 1. Defining the Surges: Covid-19 Cases in the State of Michigan. Adapted from Michigan.gov website: https://www.michigan.gov/coronavirus/0,9753,7-406-98163_98173---,00.html

The Covid-19 pandemic has unfolded in distinct surges. The figure below represents new cases of Covid-19 over time according to Michigan governmental data. Surge 1 is highlighted in red, Surge 2 in yellow, Surge 3 in blue, Surge 4 in Green, and Surge 5 in Purple.

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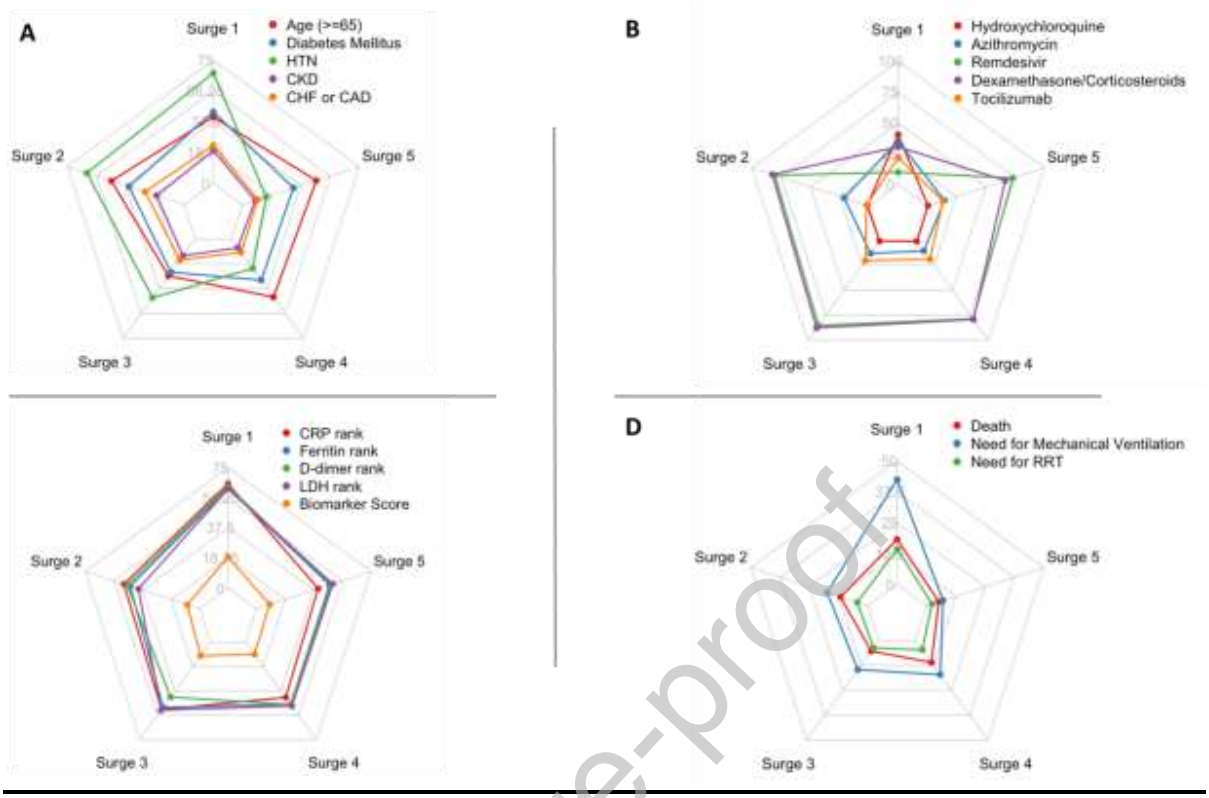

Figure 2. Radar Plots of Clinical Characteristics, Treatments, Outcomes and Inflammatory Markers Across Five Surges

In figure 2C, biomarker score refers to the composite biomarker score calculated by the summation of the leave-one-out products of the ranks of biomarkers.

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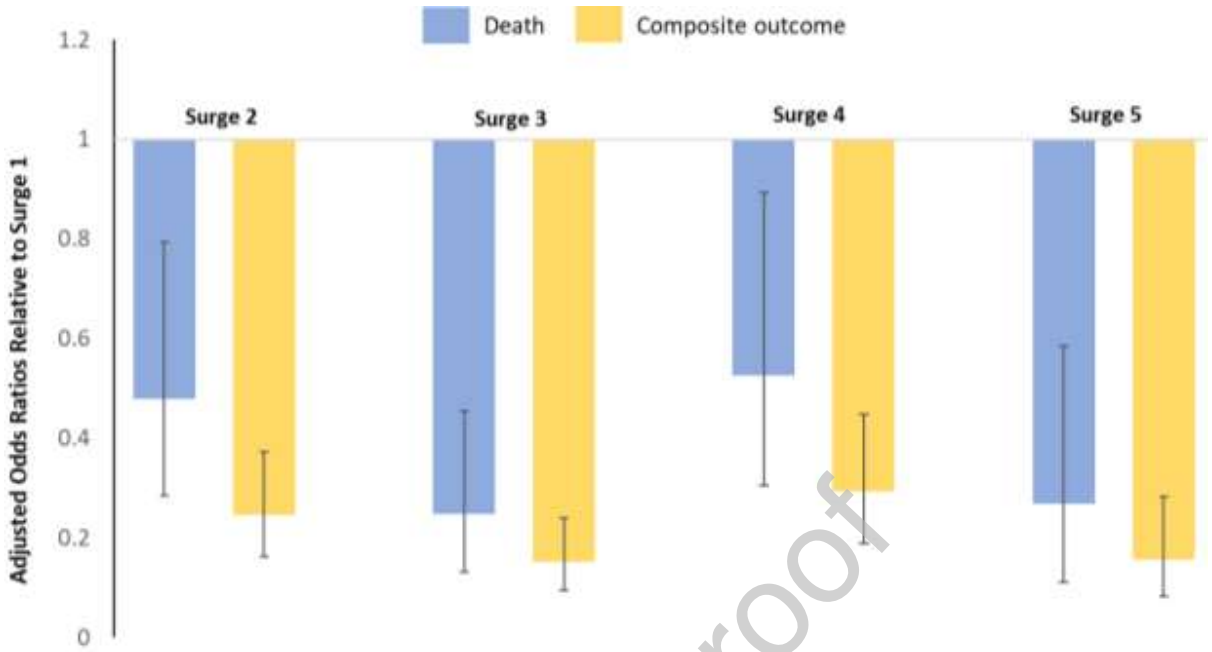

Figure 3. Binary Logistic Regression Modeling: Evaluating Surges as Independent Predictors of Outcomes

Binary logistic regression modeling with in-hospital death and the compositive outcome of death, need for mechanical ventilation, or need for renal replacement therapy as the dependent variable. Results from Model 3 are shown in the figure, which included the following independent variables: surge (subsequent surges individually relative to surge 1), patient factors (age, sex, race (white vs non-white), body mass index, hypertension, diabetes mellitus, coronary artery disease, heart failure, eGFR on admission), treatment variables (remdesivir and corticosteroids), and the composite score of biomarkers of inflammation. Graphs depict the odds ratio (OR) and 95% confidence interval for the given outcome according to each surge comparison, controlling for the aforementioned covariates.

Supplemental Table 1: Binary Logistic Regression with In-Hospital Death as Dependent Variable

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Model	Surge Comparison	Odds Ratio	95%CI	P-value
Model 0	Surge 2 vs. Surge 1	0.594	(0.428, 0.822)	0.002
	Surge 3 vs. Surge 1	0.257	(0.158, 0.404)	<0.001
	Surge 4 vs. Surge 1	0.559	(0.391, 0.793)	0.001
	Surge 5 vs. Surge 1	0.249	(0.114, 0.479)	<0.001
Model 1	Surge 2 vs. Surge 1	0.731	(0.502, 1.065)	0.103
	Surge 3 vs. Surge 1	0.377	(0.223, 0.618)	<0.001
	Surge 4 vs. Surge 1	0.773	(0.504, 1.183)	0.237
	Surge 5 vs. Surge 1	0.341	(0.149, 0.7)	0.006
Model 2	Surge 2 vs. Surge 1	0.471	(0.281, 0.78)	0.004
	Surge 3 vs. Surge 1	0.242	(0.128, 0.444)	<0.001
	Surge 4 vs. Surge 1	0.517	(0.302, 0.877)	0.015
	Surge 5 vs. Surge 1	0.255	(0.106, 0.558)	0.001
Model 3	Surge 2 vs. Surge 1	0.478	(0.285, 0.794)	0.005
	Surge 3 vs. Surge 1	0.248	(0.131, 0.455)	<0.001
	Surge 4 vs. Surge 1	0.525	(0.306, 0.893)	0.018
	Surge 5 vs. Surge 1	0.268	(0.111, 0.585)	0.002

Model 0: surge alone

Model 1: surge + patient factors (age, sex, race (white vs non-white), body-mass index, hypertension, diabetes mellitus, coronary artery disease, heart failure, and eGFR on admission)

Model 2: surge + patient factors + treatment variables (remdesivir, corticosteroids)

Model 3: surge + patient factors + treatment variables + inflammatory biomarkers composite score

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Supplemental Table 2: Binary Logistic Regression with Composite Outcome as Dependent Variable

Model	Surge Comparison	Odds Ratio	95%CI	P-value
Model 0	Surge 2 vs. Surge 1	0.301	(0.233, 0.387)	<0.001
	Surge 3 vs. Surge 1	0.207	(0.152, 0.281)	<0.001
	Surge 4 vs. Surge 1	0.318	(0.242, 0.415)	<0.001
	Surge 5 vs. Surge 1	0.146	(0.086, 0.235)	<0.001
Model 1	Surge 2 vs. Surge 1	0.38	(0.282, 0.511)	<0.001
	Surge 3 vs. Surge 1	0.234	(0.164, 0.331)	<0.001
	Surge 4 vs. Surge 1	0.436	(0.315, 0.603)	<0.001
	Surge 5 vs. Surge 1	0.206	(0.117, 0.348)	<0.001
Model 2	Surge 2 vs. Surge 1	0.242	(0.158, 0.366)	<0.001
	Surge 3 vs. Surge 1	0.149	(0.093, 0.235)	<0.001
	Surge 4 vs. Surge 1	0.288	(0.186, 0.44)	<0.001
	Surge 5 vs. Surge 1	0.151	(0.08, 0.274)	<0.001
Model 3	Surge 2 vs. Surge 1	0.246	(0.161, 0.372)	<0.001
	Surge 3 vs. Surge 1	0.151	(0.094, 0.239)	<0.001
	Surge 4 vs. Surge 1	0.292	(0.188, 0.448)	<0.001
	Surge 5 vs. Surge 1	0.155	(0.082, 0.282)	<0.001

Model 1: surge + patient factors (age, sex, race (white vs non-white), body-mass index, hypertension, diabetes mellitus, coronary artery disease, heart failure, and eGFR on admission)

Model 2: surge + patient factors + treatment variables (remdesivir, corticosteroids)

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Model 3: surge + patient factors + treatment variables + inflammatory biomarkers composite score

Composite Outcome: death, need for mechanical ventilation, or need for renal replacement therapy

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Table 1: Patient Characteristics, Inflammatory Biomarkers, Treatments, and Outcomes

Patient Characteristics	**Surge 1 (n=515)**	**Surge 2 (n=658)**	**Surge 3 (n=442)**	**Surge 4 (n=523)**	**Surge 5 (n=171)**	**P-value**
Age, mean (SD)	60.1 (15.5)	62.3 (16.3)	54.5 (16.1)	59.6 (17.3)	60.5 (17.8)	<0.001
Female, n (%)	214 (41.6)	290 (44.1)	188 (42.5)	231 (44.2)	89 (52.0)	0.191
Black, n (%)	239 (46.4)	84 (12.8)	79 (17.9)	67 (12.8)	39 (22.8)	<0.001

Body mass index, mean (SD)	32.7 (8.9)	31.5 (8.5)	33.6 (11.2)	31.4 (8.7)	30.5 (7.2)	<0.001
Diabetes mellitus, n (%)	224 (43.5)	233 (35.4)	111 (25.1)	162 (31.0)	56 (32.7)	<0.001
Hypertension, n (%)	346 (67.2)	410 (62.3)	196 (44.3)	116 (22.2)	26 (15.2)	<0.001
Coronary artery disease, n (%)	81 (15.7)	123 (18.7)	45 (10.2)	24 (4.6)	9 (5.3)	<0.001
Heart failure, n (%)	70 (13.6)	81 (12.3)	43 (9.7)	34 (6.5)	9 (5.3)	<0.001
Chronic kidney disease, n (%)	103 (20.0)	116 (17.6)	56 (12.7)	35 (6.7)	14 (8.2)	<0.001
Outside hospital transfers, n (%)	156 (30.2)	80 (12.1)	51 (11.6)	16 (3.1)	7 (4.2)	<0.001
Inflammatory Biomarkers						
C-reactive protein, median (IQR)	10.2 (13.1)	7.3 (10.1)	8.2 (9.4)	6.5 (10.0)	4.2 (7.4)	<0.001
Ferritin, median (IQR)	837 (1139)	572 (867)	678.7 (1134.2)	606.6 (904.4)	449.6 (950.3)	<0.001
Lactate dehydrogenase, median (IQR)	412 (272.5)	340 (182)	388 (225)	399 (184)	332.5 (252.5)	<0.001
D-dimer, median (IQR)	1.29 (2.0)	0.88	0.74	0.82	0.89	<0.0

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		(1.09)	(0.79)	(1.30)	(1.15)	01
Treatments						
Hydroxychloroquine, n (%)	209 (40.6)	9 (1.4)	3 (0.7)	5 (1.0)	1 (0.6)	<0.001
Azithromycin, n (%)	183 (35.5)	139 (21.1)	58 (13.1)	55 (10.5)	25 (14.6)	<0.001
Remdesivir, n (%)	52 (10.1)	529 (80.4)	377 (85.3)	412 (78.8)	125 (73.1)	<0.001
Dexamethasone/corticosteroids, n (%)	158 (30.7)	543 (82.5)	388 (87.8)	415 (79.3)	114 (66.7)	<0.001
Tocilizumab, n (%)	112 (21.7)	13 (2.0)	90 (20.4)	99 (18.9)	23 (13.5)	<0.001
Outcomes						
Death, n (%)	94 (18.3)	77 (11.7)	24 (5.4)	58 (11.1)	9 (5.3)	<0.001
Intensive care unit admission, n (%)	286 (55.5)	221 (33.6)	119 (26.9)	134 (25.6)	24 (14.0)	<0.001
Need for mechanical ventilation, n (%)	219 (42.5)	114 (17.3)	65 (14.7)	90 (17.2)	12 (7.0)	<0.001
Need for renal replacement therapy, n (%)	74 (14.4)	30 (4.6)	17 (3.8)	25 (4.8)	4 (2.3)	<0.001
Hospital length of stay (days), median (IQR)	10 (20)	6 (10)	5 (7)	6 (8)	4 (6)	<0.001

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Table 2: Multivariable Linear Regression for Inflammatory Biomarkers

Biomarker	Comparison	Estimate	C.I.	P-value
C-reactive protein	Surge 2 vs. Surge 1	-2.637	(-4.025, -1.249)	<0.001
	Surge 3 vs. Surge 1	-2.068	(-3.592, -0.543)	0.008
	Surge 4 vs. Surge 1	-3.581	(-5.104, -2.059)	<0.001
	Surge 5 vs. Surge 1	-4.685	(-6.767, -2.602)	<0.001
Ferritin	Surge 2 vs. Surge 1	-2.736	(-4.051, -1.422)	<0.001
	Surge 3 vs. Surge 1	-2.006	(-3.45, -0.562)	0.006
	Surge 4 vs. Surge 1	-2.95	(-4.392, -1.507)	<0.001
	Surge 5 vs. Surge 1	-2.88	(-4.853, -0.908)	0.004
D-dimer	Surge 2 vs. Surge 1	-5.149	(-7.132, -3.165)	<0.001
	Surge 3 vs. Surge 1	-6.388	(-8.566, -4.211)	<0.001
	Surge 4 vs. Surge 1	-4.487	(-6.663, -2.312)	<0.001
	Surge 5 vs. Surge 1	-5.005	(-7.98, -2.03)	0.001
Lactate dehydrogenase	Surge 2 vs. Surge 1	-1.835	(-2.588, -1.082)	<0.001
	Surge 3 vs. Surge 1	-0.565	(-1.392, 0.261)	0.18
	Surge 4 vs. Surge 1	-0.712	(-1.538, 0.114)	0.091
	Surge 5 vs. Surge 1	-1.09	(-2.22, 0.04)	0.059
Biomarker score[a]	Surge 2 vs. Surge 1	-7.034	(-9.477, -4.591)	<0.001
	Surge 3 vs. Surge 1	-6.050	(-8.732, -3.368)	<0.001
	Surge 4 vs. Surge 1	-7.221	(-9.901, -4.541)	<0.001
	Surge 5 vs. Surge 1	-7.411	(-11.076, -3.746)	<0.001

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[a]The Biomarker score of a patient was calculated by the summation of the leave-one-out products of the ranks (of the patient) of each biomarker, which was a combined measurement of the patient's rank of biomarkers within the cohort

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