Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Annals of Epidemiology 76 (2022) 158–164

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: sciencedirect.com/journal/annals-of-epidemiology

Original article

The impact of key secular trends during the first three waves the COVID-19 pandemic

Brian J. Lichtenstein, MD[a,*], Tyler Smith, PhD[b], Besa Smith, MPH, PhD[c], Matthew Sitzer, MA[a], Daksha Mahida, BS[a], Dan Exley, MMI[a]

[a] Sharp HealthCare, San Diego, CA, USA
[b] National University, San Diego, CA, USA
[c] Analydata, San Diego, CA, USA

ARTICLE INFO

Article history:
Received 21 February 2022
Revised 20 June 2022
Accepted 21 June 2022
Available online 29 June 2022

Keywords:
COVID-19
Hospitalization
Mortality
Epidemiology

ABSTRACT

Importance: Patient age, comorbidity burden, and disease severity at presentation are the major factors associated with surviving COVID-19. Hospital-level factors including ICU occupancy may confer additional risk to individual patients, particularly at times of maximal stress on healthcare systems. The interaction of patient- and hospital-level factors over time during pandemic disease remains an area of active exploration.
Objective: To determine the impact of patient and hospital risk factors during episodic surges, characterize severity distribution between waves, and evaluate patient-level impact of ICU capacity on COVID-19 survivorship.
Design: Retrospective cohort study.
Setting: Four acute care hospitals within an integrated healthcare network in San Diego, California.
Participants: All patients (18+ y.o.) admitted with a positive PCR test for SARS-CoV-2 or ICD-10 code for COVID-19 from March 1, 2020 through June 30, 2021.
Main Outcome(s) and Measure(s): Patient survivorship and length of stay.
Results: Six thousand eight hundred fifty-one patients were evaluated in this large cohort series. Patient level factors associated with mortality included: severity at admission (WHO Clinical Progression Score [WCPS]), age, gender, BMI, marital status, language preference, Elixhauser score, elevated laboratory (d-dimer, ferritin, LDH) or lower absolute lymphocyte count. When adjusting for patient age alone, survivorship during surges was also inversely associated with ICU occupancy, though this correlation was not present when adjusted for patient-level factors.
Conclusions and Relevance: Patient age, comorbidity burden, and severity at the time of presentation are the major factors associated with surviving COVID-19. Hospital-level factors including ICU occupancy may confer additional risk to individual patients, particularly at times of maximal stress on healthcare systems.

Following the introduction of the SARS-CoV-2 virus into human populations, the COVID-19 pandemic has been marked by episodic waves of cases, with increased community caseload followed by the specter of surges of hospitalized patients and dramatic mortality rates. While the clinical impact of the disease has been tempered by immunity from vaccination and/or prior infection [1], along with rapid advances in supportive care and pharmacologic treatment, patients who are hospitalized still face a relatively high risk of disease progression and mortality.

Much is already known about individual patient-level risk factors for severe disease and death. Age along with numerous chronic health conditions are associated with development of severe disease and death due to COVID-19 [2–4]. Environmental factors may also influence survivorship including hospital capacity, [5] COVID-19 hospital volume, [6] and ICU bed capacity [7]. Inpatient surges during pandemic COVID-19 are characteristically associated with rapid system stresses, with higher volumes and increasing percentage of patients with COVID-19 admitted in short order. In aggregate, these surge-related strains on healthcare sys-

Conflict of Interest Statement: The authors have no conflicts of interest to report as it relates to this study.

* Corresponding author: Sharp HealthCare, Department of Medicine, 2929 Health Center Drive, San Diego, CA 92123. Tel.: 858-499-2770.
E-mail address: brian.lichtenstein@sharp.com (B.J. Lichtenstein).
Social media: (B.J. Lichtenstein)

https://doi.org/10.1016/j.annepidem.2022.06.036
1047-2797/

tems may account for one in four COVID-19 deaths in the United States [8].

To better understand the impact of patient and hospital risk factors during episodic surges, characterize severity distribution between waves, and evaluate patient-level impact of ICU capacity on COVID-19 survivorship, we analyzed time to mortality independent of multiple demographics, clinical, and hospital related factors for patients hospitalized for COVID-19 at four acute care hospitals within a large integrated healthcare network (IHN) in Southern California during the first three waves of the pandemic.

Methods

Data Sources

A retrospective cohort study was performed utilizing readily available patient level information abstracted from the electronic health record (Cerner Millennium) to identify all hospitalized patients admitted with COVID-19 between March 1, 2020 and June 30, 2021 at any acute care hospital within the IHN. Patient outcomes were followed through November 30, 2021 to ensure a complete discharge status. Hospital level factors were abstracted from the submission file provided to the California Department of Public Health and the California Hospital Association daily through the study period. The study used only de-identified patient data and was approved by the IHN's institutional review board

Study Population and Covariates

Adults (aged 18+ years) who were inpatient in the IHN with a positive PCR test for SARS-CoV-2 or ICD-10 code for COVID-19 (U07.1) were included for analysis. Demographic information included age (continuous and categorized) at admission, sex, BMI (<18.5,18.5–24.9, 25–29.9, 30–34.9, 35–49.9, and ≥50) race/ethnicity (African American/Black non-Hispanic, Asian non-Hispanic, Caucasian/White non-Hispanic, Hispanic/Latin, not-reported/unknown/other), marital status (married, separated, widowed, single, divorced, unknown/missing), language (English first, English additional, non-English). Clinical information was abstracted at the patient-level and included: d-dimer (0–499, 500–999, 1000–1999, 2000–4999, ≥5000, missing), ferritin (≤400, 401–699, 700–999, 1000–1999, ≥2000, missing), LDH (≤225, 226–315, 316–499, ≥500, missing), absolute lymphocyte count (0–0.49, 0.5–0.99, 1.0–5.2, ≥5.2, missing), Hospital ICU Percent Occupancy at Admission (continuous and categorized 0–74, 75–85, 86–90, 91–95, ≥95, missing), and the presence of comorbidities as defined by Elixhauser index with van Walraven modification [9] (continuous and categorized <0, 0, 1–4, ≥5). With most variables, final disposition was available for all 6851 patients. Several variables, however, required the creation of missing categories to prevent the removal of larger numbers of patients for regression analyses where complete case analysis was completed.

WHO Clinical Progression Score (WCPS)

The WHO Clinical Progression Score segments patients with COVID-19 into categories of severity ranging from outpatient (scores 0–2), inpatient without oxygen need (score 3), low-flow oxygen (score 4), high-flow oxygen or noninvasive ventilation (score 6), or invasive mechanical ventilation without or with organ support (score 6–7 respectively) [10]. In large multisite trials, WCPS reliably segmented patients into cohorts at the time of enrollment, often with nonoverlapping mortality rates observed in patients scored between 3 and 7 [11,12]. SQL programming was utilized to assign the highest level of respiratory support for each calendar day during the hospitalization, with previously discharged patients receiving a score of "A" if discharged alive and "D" if deceased. The WCPS at admission was categorized into (3, 4, 5, 6, and 7) with those indicated with an 8 (deceased), removed for adjusted regression analyses.

Admission Waves

Patient-level information was segregated to compare 4 natural periods of the pandemic, using a nadir-to-nadir period based on total volume of hospitalized patients. This provided 4 "waves" of increased inpatient volume: wave 1 (March 1, 2020–June 6, 2020); wave 2 (June 7, 2020–October 31, 2020); wave 3 (November 1, 2020–February 28, 2021), and postwave 3 (March 1, 2021–June 30, 2021).

Statistical Analysis

Descriptive and bivariate analyses including frequencies and percentages of demographic, clinical, and hospital characteristics among study participants stratified by wave of admission were completed. Unadjusted associations between all characteristics and the wave of admission as well as the survival status were completed using Pearson Chi-Square with a $P < .05$ level of statistical significance. Unadjusted Kaplan-Meier survival estimates by wave were computed and graphed. Saturated and manual backward reduced multivariable Cox Proportional Hazards regression models were used to investigate the adjusted hazards of survival while also allowing computation of survival estimates for subgroup analyses. The Harrell's C-statistic [13] with right-censored data was used for a measure of the model's discriminatory value on a scale ranging from 0–1.0, with 0.5 being equal to chance and 1.0 being perfect prediction. Survival estimates were output stratified by wave, age, and Hospital ICU Percent Occupancy at Admission and cumulative probability of survival estimates were graphed in addition to the survival estimates. All statistical analyses were conducted using SAS (version 14.2).

Findings

The patient population of 6851 consisted of greater than 50% of patients who were 60 years of age or older. Fifty-four percent were percent men, and the majority had BMI between 18.5 and 30. Race/Ethnicity was in keeping with proportional representation in the community of COVID-19 cases [14]. There were 83% of cases were mild or moderate disease, with WCPS 3 or 4 on the day of admission. Notably 40% of patients were admitted with ICU occupancy at 90% or greater. Additional population characteristics are detailed in Table 1.

The highest proportion of patients, 62%, was admitted between November 1, 2020 and February 28, 2021 (wave 3). Unadjusted statistically significant differences (chi-square *P*-value <.05) by wave (time period admitted) were found in age (older in wave 3), BMI (higher in waves 2 and postwave 3), race/ethnicity (higher proportions of Hispanic/Latin in waves 1 and 2), marital status (higher proportions of divorced and single in postwave 3), language preference (higher proportions of non-English in waves 1 and 2), ICU stay (highest proportion in wave 1), Elixhauser score (highest in wave 1), ICU occupancy at admission (highest in wave 3), and initial WCPS at admission (highest in wave 3; Table 1). Gender was not associated with wave of admission.

Hospital utilization and patient trajectories also demonstrated secular effects. Time to progression of disease, defined as an increase in 1+ point on WCPS, remained relatively stable, with geometric mean [95% CI] of 2.6 days [2.3–2.8], 2.3 days [2.1–2.5], 2.6 days [2.5–2.7], and 2.1 days [1.9–2.3] in each successive epoch. Time to improvement, defined as a decrease in 1+ point on WCPS,

Table 1
Patient characteristics by wave

Variable	Population		Wave							
			Wave 1		Wave 2		Wave 3		Post wave 3	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Age group*	265	(3.9)	26	(3.8)	68	(5.1)	127	(3.0)	44	(7.9)
10–29										
30–39	441	(6.4)	46	(6.7)	99	(7.4)	246	(5.8)	50	(8.9)
40–49	730	(10.7)	76	(11.0)	166	(12.4)	406	(9.5)	82	(14.6)
50–59	1287	(18.8)	146	(21.2)	263	(19.6)	761	(17.9)	117	(20.9)
60–69	1612	(23.5)	164	(23.8)	307	(22.8)	1,013	(23.8)	128	(22.9)
70–79	1286	(18.8)	114	(16.5)	219	(16.3)	874	(20.5)	79	(14.1)
80–89	886	(12.9)	88	(12.8)	166	(12.4)	587	(13.8)	45	(8.0)
90+	344	(5.0)	29	(4.2)	56	(4.2)	244	(5.7)	15	(2.7)
Gender	3188	(46.5)	315	(45.7)	637	(47.4)	1,960	(46.0)	276	(49.3)
Female										
Male	3663	(53.5)	374	(54.3)	707	(52.6)	2,298	(54.0)	284	(50.7)
BMI category*	279	(4.1)	16	(2.3)	32	(2.4)	212	(5.0)	19	(3.4)
<18.5										
18.5–24.9	1459	(21.3)	147	(21.3)	264	(19.6)	936	(22.0)	112	(20.0)
25–29.9	2089	(30.5)	224	(32.5)	417	(31.0)	1,298	(30.5)	150	(26.8)
30–34.9	1526	(22.3)	177	(25.7)	304	(22.6)	904	(21.2)	141	(25.2)
35–39.9	772	(11.3)	56	(8.1)	178	(13.2)	470	(11.0)	68	(12.1)
40+	726	(10.6)	69	(10.0)	149	(11.1)	438	(10.3)	70	(12.5)
Race/Ethnicity*	280	(4.1)	23	(3.3)	54	(4.0)	163	(3.8)	40	(7.1)
African American/Black										
Asian	492	(7.2)	32	(4.6)	75	(5.6)	349	(8.2)	36	(6.4)
Caucasian/White	1504	(22.0)	110	(16.0)	221	(16.4)	1,017	(23.9)	156	(27.9)
Hispanic/Latin	3609	(52.7)	448	(65.0)	797	(59.3)	2,133	(50.1)	231	(41.3)
Not reported, unknown, other	966	(14.1)	76	(11.0)	197	(14.7)	596	(14.0)	97	(17.3)
Marital status*	3050	(44.5)	311	(45.1)	593	(44.1)	1,915	(45.0)	231	(41.3)
Married										
Separated	244	(3.6)	25	(3.6)	53	(3.9)	149	(3.5)	17	(3.0)
Widowed	891	(13.0)	86	(12.5)	170	(12.6)	584	(13.7)	51	(9.1)
Single	1796	(26.2)	186	(27.0)	348	(25.9)	1,082	(25.4)	180	(32.1)
Divorced	599	(8.7)	49	(7.1)	122	(9.1)	372	(8.7)	56	(10.0)
Unknown/missing	271	(4.0)	32	(4.6)	58	(4.3)	156	(3.7)	25	(4.5)
Language*	4098	(59.8)	362	(52.5)	739	(55.0)	2,596	(61.0)	401	(71.6)
English first										
English additional	476	(6.9)	54	(7.8)	99	(7.4)	294	(6.9)	29	(5.2)
Non-English	2277	(33.2)	273	(39.6)	506	(37.6)	1,368	(32.1)	130	(23.2)
ICU stay*	5173	(75.5)	415	(60.2)	948	(70.5)	3,397	(79.8)	413	(73.8)
No										
Yes	1678	(24.5)	274	(39.8)	396	(29.5)	861	(20.2)	147	(26.3)
Elixhauser score*	642	(9.4)	53	(7.7)	127	(9.4)	408	(9.6)	54	(9.6)
Less than 0										
0	1072	(15.6)	88	(12.8)	198	(14.7)	697	(16.4)	89	(15.9)
1–4	886	(12.9)	109	(15.8)	200	(14.9)	490	(11.5)	87	(15.5)
5 or more	4251	(62.0)	439	(63.7)	819	(60.9)	2,663	(62.5)	330	(58.9)
Score at admission*	2127	(31.0)	207	(30.0)	483	(35.9)	1,240	(29.1)	197	(35.2)
3										
4	3552	(51.8)	354	(51.4)	632	(47.0)	2,307	(54.2)	259	(46.3)
5	777	(11.3)	52	(7.5)	144	(10.7)	519	(12.2)	62	(11.1)
6–7	395	(5.8)	76	(11.0)	85	(6.3)	192	(4.5)	42	(7.5)

* $p < 0.05$

decreased throughout the each period with geometric mean [95% CI] of 4.6 days [4.1–5.2], 4.3 days [3.9–4.6], 3.3 days [3.1–3.5], and 2.8 days [2.4–3.2]. Length of stay similar improved, with geometric mean of wave 1 at 7.9 days [7.3–8.5], wave 2 at 6.4 days [6.1–6.7], wave 3 at 5.4 days [5.2–5.5], postwave 3 at 4.8 days [4.4–5.2].

The univariate and bivariate mortality experience of the patient population of 6851 was 1160 (17.0%) deceased or discharged to inpatient hospice (mortality). Unadjusted statistically significant differences (chi-square *P*-value <.05) in mortality (yes/no) were found between waves, with additional significant differences in mortality, WCPS at admission, age, gender, BMI, marital status, language preference, Elixhauser score, ICU, and occupancy at admission. Patients with elevated laboratory (d-dimer, ferritin, LDH) or lower absolute lymphocyte count had significantly higher mortality when compared to patients with normal values. Race/ethnicity was not associated with mortality in this bivariate analysis.

In the multicollinearity investigation, there were no variables exhibiting collinearity as measured with a variance inflation level of ≥4.0. Saturated and reduced multivariable Cox Proportional regression analysis results are reported in Supplemental Table 1. There was little difference in measures of effect between the saturated and reduced models suggesting minimal adjustment with wave being left in the final model even though the overall *P*-value was not <.05.

In the reduced model, those admitted in wave 3 were at 1.14 times the risk of mortality when compared with those admitted in wave 1 though the finding was not statistically significant (adjusted hazard ratio [AHR] = 1.14; 95% CI = 0.93–1.39). After adjusting for all other variables in the model, those who were 90 years of age or older were at 13 times the risk of mortality when compared to those less than 30 (AHR = 13.01; 95% CI = 5.23–32.39). Patients who had a BMI <18.5 were at 1.5 times the risk of mor-

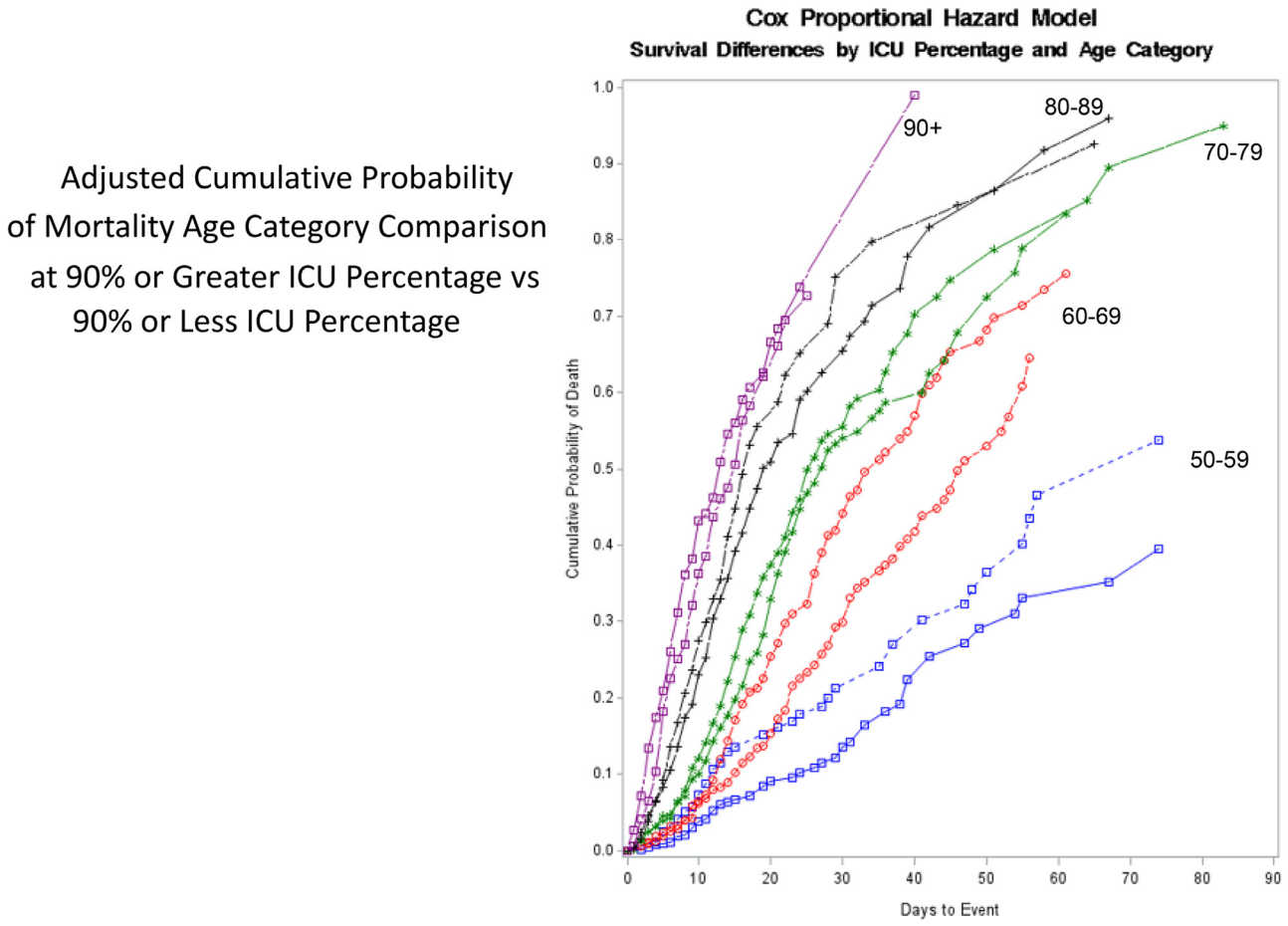

Fig. 1. Survival difference by ICU occupancy, stratified by age. Adjusted cumulative probability of mortality or discharge to hospice, stratified by age, comparing ICU capacity and 90% or greater vs less than 90%.

tality when compared to those with a normal BMI (AHR = 1.49; 95% CI = 1.17–2.91), and those who were divorced (AHR = 0.73) or widowed (AHR = 0.83) were at lower risk when compared to those who were married. After adjusting for all other variables in the model, those who had an Elixhauser score of 5 or more had 1.70 times the risk of mortality when compared to those with a score of 0 (AHR = 1.70; 95% CI = 1.23–2.34) and those with a WCPS of 6 or 7 at admission had 2.44 times the risk of mortality when compared to those with a score of 3 (AHR = 2.44; 95% CI = 1.91–3.12). Those with d-dimer ≥5000 (AHR = 1.53; 95% CI = 1.13–2.07), ferritin ≥2000 (AHR = 1.36; 95% CI = 0.98–1.89), LDH ≥500 (AHR = 2.64; 95% CI = 1.75–3.98), and absolute lymphocyte count ≥5.2 (AHR = 1.45; 95% CI = 0.53–3.97) were at increased adjusted risk when compared to patients with labs in the reference range.

The corresponding cumulative probability plots of mortality by wave remained stable and parallel over the follow-up period though there was a divergence which suggests a temporal effect of the time-period (Fig. 1). Though time differences are shown in the figure, with wave 3 having the highest probability of mortality, there was no statistically significant interaction between wave and time when tested.

Sensitivity analyses of age and percent ICU occupancy at admission were also conducted. Patients admitted when ICU occupancy was at 90%–94.9% were at 1.60 times the risk of mortality (unadjusted HR = 1.60; 95% CI = 1.04–2.45) while those admitted when the ICU occupancy was at ≥95% were at 1.43 times the risk (unadjusted HR=1.43; 95% CI=0.94 to 2.18) when compared to patients admitted to the ICU occupancy at less than 50% occupancy. When restricting the patient population to those admitted when the ICU occupancy was at ≥90%, the unadjusted risk doubled for each age group. Risk in those aged 50–59 went from 1.80 in the full patient population to 3.51 for those admitted when the ICU occupancy was at 90%. Risk in those age 60–69 went from 3.21–5.99; 70–79 went from 4.91–9.72; 80–89 went from 9.82–18.83; and ≥90 went from 17.54–31.92 (data not shown). Visual inspection of the cumulative probability plots of mortality by age category over the follow-up period suggests a temporal effect of the time-period (Fig. 2) and a clear difference in risk in age categories for those admitted when the ICU occupancy was ≥90%.

Discussion

Our findings demonstrate survivorship of COVID-19 is most strongly associated with younger age, lack of comorbidities, and severity of illness at the time of presentation to the hospital. Notably, we observed a shift in the severity of patient admitted to the IHN hospitals between waves, with a significantly higher proportion of critical cases (WCPS 5 through 7) observed in wave 3 (Fig. 2), that is not readily explained by demographic shifts, comorbidity burden, or the predominant SARS-CoV-2 strain during each wave (waves 1 through 2 were predominantly wild-type and later S:D614G strains; wave 3, Epsilon; and post-wave 3, Alpha) [15]. We do not have a ready explanation other than it is possible patients presented with more advanced disease—be it from denial of illness, concern about their own use of scarce resources, caring for family members who are also ill, socioeconomic insecurity, etc.—and hence imparted spectrum bias with on-average sicker patients during peak hospital demand. Akin to other reports we found that Race/Ethnicity were not associated with survivor-

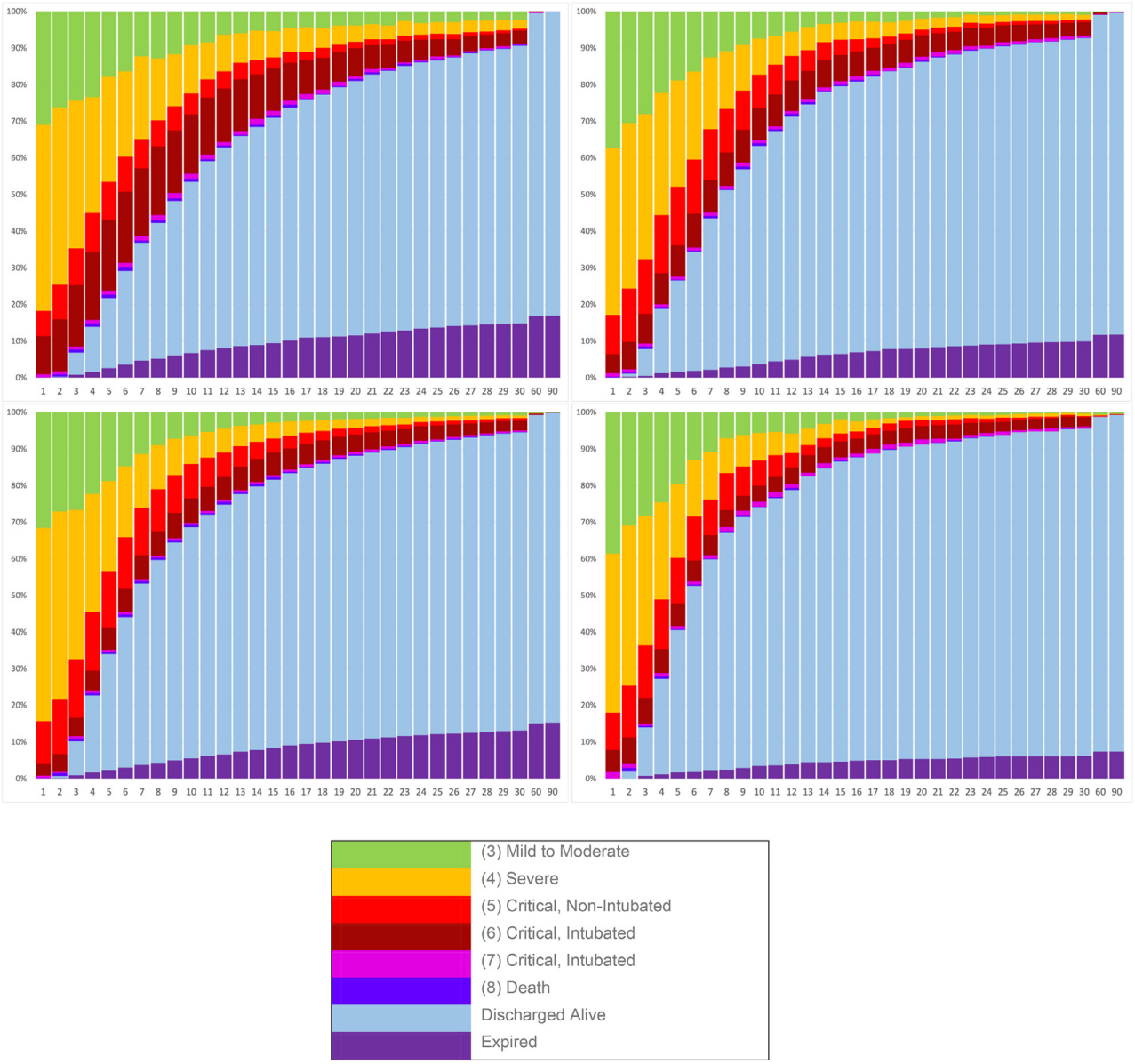

Fig. 2. Patient severity distribution presented as a cumulative time series. Each patient's daily WHO Clinical Progression Score is normalized to the day of hospitalization. Those who were discharged are maintained in the cohort over time. Patients are grouped by admission date, segmenting into four natural periods during the first 1.5 year of the COVID-19 pandemic: wave 1 (top-left), wave 2 (top-right), wave 3 (bottom-left), postwave 3 (bottom right). WCPS: 3 (green), 4 (yellow), 5 (red), 6 (dark red), 7 (magenta), 8 (blue) discharge alive (light blue), discharged deceased (purple).

ship when accounting for other patient factors (age, Elixhauser score, and severity in particular) [16,17] in this insured and predominantly managed care population. In this cohort obesity, as defined by BMI, was also not associated with mortality after adjusting for other covariates.

We also observed that when adjusting for patient age alone, survivorship during surges is also inversely associated with ICU occupancy on admission, though this correlation is not present when accounting for additional patient-level factors—most notably severity on the time of admission (WCPS on day 1). While surge dynamics and hospital strain are very likely to impact patient care, particular when ICU occupancy is at its higher, [1,18,19] a single measure of hospital strain (ICU occupancy on admission) may not be a sensitive enough to assess the additive mortality risk factor for patients admitted to the hospital with COVID-19. However in light of well-executed population-level studies that continue to demonstrate inverse relationships between community caseload, resource scarcity and survivorship during the pandemic, [6,7,20] hospitals and communities would be well advised to consider the additive mortality risk imposed by surges. Together, this dynamic interaction of patient, pathogen, and hospital-level factors need to be considered when understanding the course of the pandemic at both the individual and group level (Fig. 3)—particularly in light of growing population immunity and changes to virulence as novel strains arise [21,22].

Unique among inpatient studies, outcomes are available for all cohort participants—including a time series of severity for every patient on every hospital day. This provides unique insights not only on hard outcomes, but intermediate measures of illness trajectories and by proxy resource utilization and bed allocations for each epoch under investigation. Using this approach, we are readily able to demonstrate that each sequential wave also brought improvements with clinical outcomes, with decreasing length of stay and time to improvement over the study period.

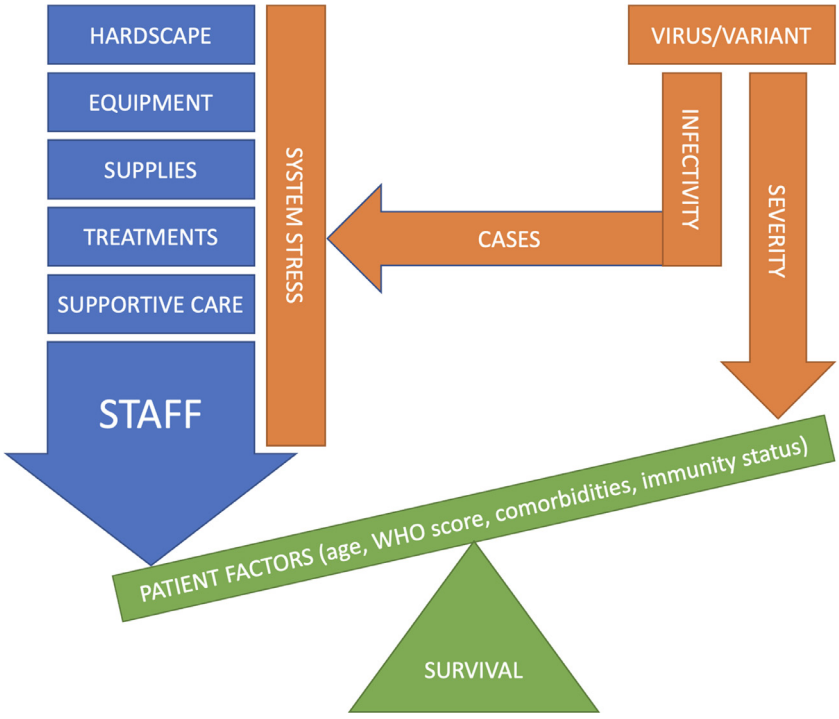

Fig. 3. Conceptual model of COVID-19 outcomes and impact of surges patient and system-level factors impact survivorship during pandemic illness. While patient-level factors are most easily studied, the context of care and pathogen-related characteristics remain critical and less well-understood elements that impact outcomes.

A major shortfall in our dataset is the unknown vaccination status of patients. While this is likely to have minimal impacts in waves 1 through 3 when most of the population was not eligible for vaccination, vaccination status is also likely to be associated with other health-seeking and risk-reduction behaviors. More directly, immunization confers significant risk reduction against symptomatic disease, even among breakthrough cases that are ultimately hospitalized, [23] and thus remains an important and unmeasured confound.

Receipt of disease-modifying pharmacotherapy and other supportive measures was also not directly assessed in this study. Numerous classes of drug impact survivorship and risk of disease progression, and while we are confident the vast majority of hospitalized patients received best-practice care during their hospitalization, implementation of evolving biomedical science remains a challenging measure and an even more difficult one to study. The aggregate impact of evolving treatments is only accounted indirectly via our secular covariate ("waves"), coinciding with the advent of routine use of prophylactic or intermediate dose anticoagulation and remdesivir [24] (wave 1), corticosteroids [12] (wave 2), anti-IL6 [25], and JAK inhibitors [26,27] (wave 4).

Beyond patient-level factors, in this work we are unable to elucidate whether hospital-level factors represent direct and/or indirect environmental risk during surges. Staffed bed occupancy is but one of many challenges faced by hospital teams during surges; additional unmeasured confounds such as staffing and provider availability, patient to staff/provider ratios, equipment utilization, pharmaceutical availability, etc., were episodically impacted as well but remain unmeasured in this work. In addition, any COVID-related deaths that occurred without hospitalization were not included in this analysis.

Future Directions

In the face of an evolving pathogen and shifts in population-level immunity, we strongly encourage organizations and governments to enhance minimum reporting standards, by adding measures of disease severity, immunity status (both through vaccination and confirmed prior infection), and when possible, link individual cases to viral genotype to elucidate the complex interplay of patient, treatment, and pathogen.

Conclusions

Patient age, comorbidity burden, and severity at the time of presentation are the major factors associated with surviving COVID-19. ICU occupancy may confer additional risk to individual patients, particularly at times of maximal stress on healthcare systems, though the direct or indirect impacts on patient survivorship and disease trajectory remains difficult to disentangle from patient-level factors and may be smaller than previously reported. Host immunity and pathogen virulence remain in ongoing interplay as a novel virus continues to infect the human population; and hence additional information regarding prior infection and/or vaccination history as well as SARS-CoV-2 variant genotype remains a critical piece to understand the evolving risk from this pathogen. These findings demonstrate the need for nuanced interpretations of hospitalized patient outcomes in the face of major secular trends during the pandemic, namely: shifting patient demographics, ongoing improvements in treatment, episodic health system strains, shifts in population immunity, and novel variants.

Acknowledgments

We are deeply appreciative to the insights provided by our clinician partners, as well as industrious and thorough work from our teammates in health informatics and data science, including Christopher Tomac, Youyang Gu, and Paul Sterk. All project funding for this work was provided through routine salary support for the authors at Sharp HealthCare, as well as grant from the Sharp HealthCare Foundation which supported statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.annepidem.2022.06.036.

References

[1] Wilde H, Mellan T, Hawryluk I, et al. The association between mechanical ventilator availability and mortality risk in intensive care patients with COVID-19: a national retrospective cohort study. BMC Medicine 2021;19(213). doi:10.1186/s12916-021-02096-0.

[2] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA - J Am Med Assoc 2020;323(13):1239–42. doi:10.1001/jama.2020.2648.

[3] Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ 2020:369. doi:10.1136/bmj.m1966.

[4] Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance — United States, January 22–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(24):759–65. doi:10.15585/mmwr.mm6924e2.

[5] Karaca-Mandic P, Sen S, Georgiou A, Zhu Y, Basu A. Association of COVID-19-related hospital use and overall COVID-19 mortality in the USA. J Gen Intern Med 2020:1–3 Published online August 19. doi:10.1007/s11606-020-06084-7.

[6] Block BL, Martin TM, Boscardin WJ, et al. Variation in COVID-19 mortality across 117 US hospitals in high- and low-burden settings. J Hosp Med 2021;17:2021. doi:10.12788/jhm.3612.

[7] Janke AT, Mei H, Rothenberg C, Becher RD, Lin Z, Venkatesh AK. Analysis of hospital resource availability and COVID-19 mortality across the United States. J Hosp Med 2021;16(Issue 2021-Jan online first):E1–4. doi:10.12788/jhm.3539.

[8] Kadri SS, Sun J, Lawandi A, et al. Association between caseload surge and COVID-19 survival in 558 U.S. hospitals, March to August 2020. Ann Intern Med 2021 Published online July 6. doi:10.7326/M21-1213.

[9] Van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 2009;47(6):626–33. doi:10.1097/MLR.0b013e31819432e5.

[10] Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192–7. doi:10.1016/S1473-3099(20)30483-7.

[11] REMAP-CAP Investigators, ACTIV-4a Investigators, ATTACC InvestigatorsTherapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med 2021;385(9):777–89. doi:10.1056/NEJMoa2103417.

[12] Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med 2020;384:693–704 Published online July 17. doi:10.1056/nejmoa2021436.

[13] Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. Stat Med 1984;3(2):143–52. doi:10.1002/sim.4780030207.

[14] County of San Diego Health and Human Services. County of San Diego 2019 Novel Coronavirus (COVID-19) race/ethnicity summary. Published 2021. Accessed August 12, 2021. https://www.sandiegocounty.gov/content/dam/sdc/hhsa/programs/phs/Epidemiology/COVID-19 Deaths by Demographics.pdf

[15] San Diego, California, United States Variant Report. Accessed December 9, 2021. https://outbreak.info/location-reports?loc=USA_US-CA_06073

[16] Navar AM, Purinton SN, Hou Q, Taylor RJ, Peterson ED. The impact of race and ethnicity on outcomes in 19,584 adults hospitalized with COVID-19. Stepkowski S, ed. PLoS One 2021;16(7):e0254809. doi:10.1371/journal.pone.0254809.

[17] Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. Ann Intern Med 2020;M20(3742) Published online August 12. doi:10.7326/m20-3742.

[18] Yergens DW, Ghali WA, Faris PD, Quan H, Jolley RJ, Doig CJ. Assessing the association between occupancy and outcome in critically Ill hospitalized patients with sepsis. BMC Emerg Med 2015;15(1):31. doi:10.1186/s12873-015-0049-y.

[19] Harris S, Singer M, Rowan K, Sanderson C. Delay to admission to critical care and mortality among deteriorating ward patients in UK hospitals: a multicentre, prospective, observational cohort study. Lancet 2015;385:S40. doi:10.1016/s0140-6736(15)60355-5.

[20] Asch DA, Sheils NE, Islam MN, et al. Variation in US hospital mortality rates for patients admitted with COVID-19 during the first 6 months of the pandemic. JAMA Intern Med 2020;181(4):471–8 Published online December 22. doi:10.1001/jamainternmed.2020.8193.

[21] Fisman DN, Tuite AR. Evaluation of the relative virulence of novel SARS-CoV-2 variants: a retrospective cohort study in Ontario, Canada. Can Med Assoc J 2021;193(42):E1619–25. doi:10.1503/cmaj.211248.

[22] Taylor CA, Patel K, Pham H, et al. Severity of disease among adults hospitalized with laboratory-confirmed COVID-19 before and during the period of SARS-CoV-2 B.1.617.2 (Delta) predominance — COVID-NET, 14 states, January–August 2021. MMWR Morb Mortal Wkly Rep 2021;70(43):1513–19. doi:10.15585/mmwr.mm7043e1.

[23] Tenforde MW, Self WH, Adams K, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. Jama 2021:30329. doi:10.1001/jama.2021.19499.

[24] Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020;383(19):1813–26. doi:10.1056/nejmoa2007764.

[25] Landray M. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. Lancet 2021;397(10285):1637–45 Published online February 112021.02.11.21249258. doi:10.1016/S0140-6736(21)00676-0.

[26] Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for hospitalized adults with Covid-19. N Engl J Med 2020;384:795–807 Published online December 11NEJMoa2031994. doi:10.1056/NEJMoa2031994.

[27] Marconi VC, Ramanan A V, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet 2021;9(12):1407–18. doi:10.1016/S2213-2600(21)00331-3.