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Variation in Use of Repurposed Medications Among Patients With Coronavirus Disease 2019. From The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study: Coronavirus Disease 2019 Registry Investigator Group

IMPORTANCE: At the start of the coronavirus disease 2019 pandemic, medications repurposed for management of coronavirus disease 2019 were used in the absence of clinical trial evidence.

OBJECTIVES: To describe the variation and evolution in use of repurposed medications for coronavirus disease 2019.

DESIGN, SETTING, AND PARTICIPANTS: Observational cohort study of adults hospitalized with coronavirus disease 2019 between February 15, 2020, and April 12, 2021, across 76 United States and international hospitals within the Society of Critical Care Medicine's Discovery Viral Infection and Respiratory Illness Universal Study coronavirus disease 2019 registry.

MAIN OUTCOMES AND MEASURES: Hospital variation was quantified using multivariable adjusted random effects logistic regression models and unsupervised clustering. Repurposed medications included antivirals, corticosteroids, hydroxychloroquine, immunomodulators, and therapeutic dose anticoagulants.

RESULTS: Among 7,069 adults hospitalized with coronavirus disease 2019, 1,979 (28%) received antivirals, 2,876 (41%) received corticosteroids, 1,779 (25%) received hydroxychloroquine, 620 (9%) received immunomodulators, and 2,154 (31%) received therapeutic dose anticoagulants. Contribution of hospital site to risk-adjusted variation was 46% for antivirals, 30% for corticosteroids, 48% for hydroxychloroquine, 46% for immunomodulators, and 52% for therapeutic dose anticoagulants. Compared with the early pandemic, the later pandemic practice phenotypes converged with increased use of antivirals (odds ratio, 3.14; 95% CI, 2.40–4.10) and corticosteroids (odds ratio, 5.43; 95% CI, 4.23–6.97), with decreased use of hydroxychloroquine (odds ratio, 0.02; 95% CI, 0.01–0.04) and immunomodulators (odds ratio, 0.49; 95% CI, 0.34–0.70). There was no clinically significant change in the use of therapeutic dose anticoagulants (odds ratio, 1.01; 95% CI, 1.01–1.02). There were no differences in risk-adjusted mortality between hospitals with high rates of repurposed medication use compared with hospitals with low rates of use.

CONCLUSIONS AND RELEVANCE: Hospital variation in the use of repurposed medications varied widely across hospitals early in the pandemic and later converged with the emergence of randomized clinical trials. Platforms developed for rapid activation and enrollment in clinical trials of repurposed medications are needed prior to the next pandemic to expedite effective, evidence-based practice.

KEY WORDS: antiviral agents; coronavirus disease 2019; dexamethasone; hydroxychloroquine; Viral Infection and Respiratory Illness Universal Study

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The rapid spread and high mortality associated with coronavirus disease 2019 (COVID-19) generated an urgency to identify effective therapeutics. The long research and development timelines associated with novel therapeutics prompted some clinicians to use repurposed medications, with existing safety data, for treatment of COVID-19 infection in the absence of randomized controlled trial (RCT) evidence. Due to the lack of evidence-based guidelines, use of repurposed medications was likely driven by clinician preference, hospital policy and culture, and evolving evidence. Practice patterns for medications repurposed for management of patients with COVID-19 over time have not been well-characterized. The objective of this international, observational study of patients hospitalized with COVID-19 was to describe hospital-level variation in the use of repurposed medications, to explore how medication practice patterns changed over the course of the pandemic, and to characterize the impact of practice variation on mortality risk. We hypothesized that use of repurposed medications varied widely in the early stages of the pandemic with disparate mortality risk, with more uniform practice patterns and mortality risk emerging as clinical trial evidence became available.

MATERIALS AND METHODS

Data Source and Data Collection

The Society of Critical Care Medicine's Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS) COVID-19 Registry (NCT04323787) is an observational, global database of adult and pediatric patients hospitalized with COVID-19 consisting of data from 300 participating sites across 27 countries. The VIRUS registry was approved by the Mayo Clinic (20-002610) and Boston University (H-40009) institutional review boards with local institutional review board approval obtained by participating sites (1, 2). Waiver of informed consent was used with entry of de-identified data of patients hospitalized with COVID-19 using Research Electronic Data Capture, a secure web-based software and workflow methodology for electronic collection and management research data (3, 4). Patients were followed from hospital admission until hospital discharge or death.

Study Population

Eligible participants included adults (age ≥ 18 yr) hospitalized with confirmed COVID-19 infection between February 15, 2020, and April 12, 2021, using The Society of Critical Care Medicine Discovery VIRUS COVID-19 Registry (NCT04323787). We excluded hospitals that enrolled fewer than 10 total patients in the registry (to stabilize estimates of medication practice), that did not engage with the medication data entry questions in the registry (i.e., by leaving data blank and not selecting "none" if no repurposed medications were selected) (5), and that documented fewer than 80% of patient outcomes data (to focus on hospitals with higher quality data collection).

Exposures, Outcomes, and Covariates

The primary exposure of interest was the hospital site of admission. The primary outcomes of interest were the hospital-level variation in use of medications repurposed for the management of patients hospitalized with COVID-19. We examined commonly used repurposed drug classes in the Registry including: 1) antivirals (a composite of interferon-alpha, interferon-beta, lopinavir, neuraminidase inhibitors, remdesivir, ribavirin, ritonavir); 2) corticosteroids; 3) hydroxychloroquine; 4) immunomodulators (a composite of interleukin-6 inhibitors, anakinra, Janus kinase inhibitors); and 5) therapeutic dose anticoagulants. Medication receipt was defined if the patient received the medication of interest at least once during the index hospitalization without further characterization on duration or timing. Patients who received multiple different medications during their hospitalization were included in all appropriate medication categories, which were not mutually exclusive.

Covariates of interest included hospital characteristics (i.e., geographic location) and patient characteristics (i.e., patient demographics, comorbid conditions, prehospital medications, admission code status, ICU admission, admission Sequential Organ Failure Assessment score [6]). Results were stratified based on two possible time periods of hospital admission: 1) the early stage of the pandemic (i.e., from February 15, 2020, to June 30, 2020) when little trial evidence existed and 2) the mid-late stage of the pandemic (i.e., from July 1, 2020, to April 12, 2021) when clinical trial evidence emerged (7–14).

Statistical Analysis

Dichotomous and categorical variables were summarized using counts with percentages. Continuous variables were summarized using mean with SD or median with interquartile range (IQR) based on the distribution. Multilevel random effects logistic regression models, with each hospital included as a random intercept, were used to determine multivariable adjusted associations between patient and hospital characteristics with repurposed medication use. Variation in use of each individual medication was quantified by the intraclass correlation coefficient (ICC) and the median odds ratio (OR) (15). The ICC quantifies the variation in medication use attributed to the hospital site after adjusting for patient- and hospital-level factors. The median OR represents the median increase in odds of receiving a medication if a theoretical individual moves from a randomly selected hospital with lower use to a hospital with higher use.

To explore medication practice pattern similarities across hospitals, we used the unsupervised Clustering Large Applications (CLARA) algorithm (16) to identify hospital-level medication practice pattern clusters. Medication practice clusters were identified by calculating the proportion of patients by hospital who received each medication of interest and then using CLARA to group hospitals with similar rates of medication use. The optimal number of clusters was chosen to maximize the average silhouette width (17) that identifies how well-matched hospitals are within their selected cluster and how poorly matched they are to hospitals outside their cluster. Each cluster represents hospitals with a distinct set of medication practice patterns encompassing the five repurposed medications of interest. Sensitivity analysis was performed for unsupervised clustering analysis using the elbow method (18) for optimal cluster size validation.

An exploratory analysis was performed to evaluate the association of hospital medication practice phenotypes with mortality risk using multivariable logistic regression models. To allow for effective comparisons during the early pandemic stage, hospitals were categorized as experimental if they exhibited routine repurposed medication use compared with conservative hospitals that did not routinely use repurposed medications. Routine use was defined as greater than 50% use of any of the repurposed medications of interest. During the later pandemic stage, risk-adjusted mortality was assessed using the clusters defined by CLARA analysis as the experimental hospital practice categorization was not feasible with the arrival of clinical trial evidence.

Missing data in the registry could not be considered missing completely at random, and missing data were not imputed. Complete case analysis was used for the mixed effect models where covariate data was missing to minimize the risk of "incomplete outcome data bias" (19). Statistical analyses were conducted using SAS (Version 9.4; Cary, NC) and R (Version 4.1.0; R Core Team).

RESULTS

Among 8,840 adult patients admitted with COVID-19 from hospitals that engaged with the VIRUS registry during the study period, 7,069 patients (80%) across 76 participating hospital sites were included in the study (**Fig. 1**). Patients had a median age of 61 years (IQR, 48–72 yr), 42% were female, 42% were White, and 23% were Black or African American and 63% were admitted to U.S.-based hospitals (**Table 1** and [Extended patient and hospital characteristics are seen in **Supplemental Table 1**, http://links.lww.com/CCX/A831]). Of the 7,069 patients hospitalized with COVID-19, 1,979 (28%) received antivirals, 2,876 (41%) received corticosteroids, 1,779 (25%) received hydroxychloroquine, 620 (9%) received immunomodulators, and 2,154 (31%) received therapeutic dose anticoagulants.

Practice Variation in Repurposed Medication Use

The crude median hospital-level use of repurposed medications was 21% (IQR, 6–48%) for antivirals, 38% (IQR, 20–63%) for corticosteroids, 14% (IQR, 5–45%) for hydroxychloroquine, 6% (IQR, 0–12%) for immunomodulators, and 27% (IQR, 8–49%) for therapeutic dose anticoagulants. The median OR for receipt of antivirals was 4.88 (95% CI, 1.28–18.39), representing the median increase in odds of receiving antivirals when being treated at a "high antiviral use" hospital compared with a "low antiviral use" hospital. Similarly, the median OR was 3.09 (95% CI, 1.52–6.25) for corticosteroids, 5.27 (95% CI, 1.15–23.73) for hydroxychloroquine, 4.90 (95% CI, 1.02–23.24) for immunomodulators, and 5.95 (95% CI, 1.25–27.84) for therapeutic dose anticoagulants. The variation in medication use contributed to by the hospital site of admission (ICC) was 46% for antivirals, 30%

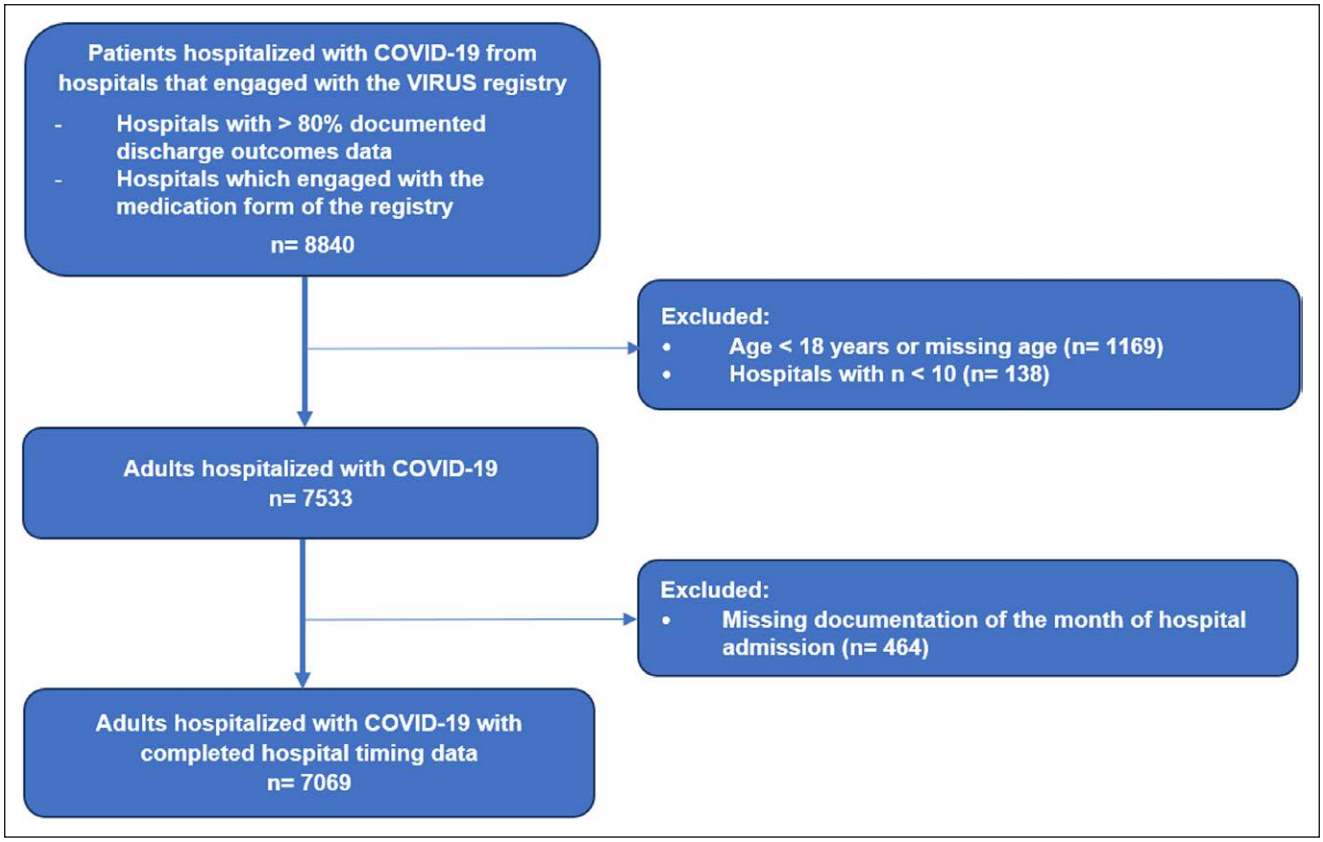

Figure 1. Cohort assembly of adults hospitalized with coronavirus disease 2019 (COVID-19) infection. VIRUS = Viral Infection and Respiratory Illness Universal Study.

for corticosteroids, 48% for hydroxychloroquine, 46% for immunomodulators, and 52% for therapeutic dose anticoagulants. Compared with the early pandemic stage, the mid-late pandemic stage was associated with significantly increased use of antivirals (adjusted OR, 3.14; 95% CI, 2.40–4.10), corticosteroids (adjusted OR, 5.43; 95% CI, 4.23–6.97), and therapeutic dose anticoagulants (adjusted OR, 1.01; 95% CI, 1.01–1.02), and a decrease in use of hydroxychloroquine (adjusted OR, 0.02; 95% CI, 0.01–0.04) and immunomodulators (adjusted OR, 0.49; 95% CI, 0.34–0.70). Multivariable adjusted associations between patient- and hospital-level characteristics with repurposed medication receipt are seen in **Supplemental Table 2** (http://links.lww.com/CCX/A832).

Repurposed Medication Clusters of Practice

Cluster analysis involved evaluation of 59 hospitals during the early pandemic stage and 32 hospitals during the mid-late pandemic stage. CLARA identified nine practice pattern clusters in the early pandemic stage cohort and two in the mid-late pandemic stage cohort (**Supplemental Fig. 1**, http://links.lww.com/CCX/A830). The medication prescription patterns in the early and mid-late pandemic stages are shown in **Table 2**. The early pandemic stage clusters had highly variable medication practices with hospital composition within each cluster ranging from three to 11 hospitals. In the mid-late pandemic stage cohort, the two medication practice patterns included: (cluster 1: 28 hospitals) with high antiviral use and corticosteroid use; (cluster 2: four hospitals) with high corticosteroid, immunomodulator, and therapeutic anticoagulant use, but no antiviral use (Table 2). The average silhouette width for unsupervised clustering of the early pandemic stage cohort was 0.22, suggesting poor cohesion of hospital medication practice patterns within clusters compared with hospitals in other medication practice pattern clusters (**Supplemental Figs. 2** and **3**, http://links.lww.com/CCX/A830). Comparatively, the average silhouette width for unsupervised clustering of the mid-late pandemic stage cohort was 0.43, which implies more cohesive medication practice patterns of hospitals within a

TABLE 1.
Patient Characteristics and Repurposed Medication Practice Stratified by Pandemic Stage

Characteristics	Overall	Pandemic Stage	
		Early: February 2020–June 2020	Mid-Late: July 2020–April 2021
n (%)	7,069 (100)	4,086 (58)	2,983 (42)
Hospital site, *n* (%)			
United States	4,460 (63)	2,789 (69)	1,671 (56)
International	2,580 (37)	1,277 (31)	1,303 (44)
Highest oxygenation support received, *n* (%)			
None (i.e., room air)	1,298 (18)	790 (19)	508 (17)
Nasal cannula/face mask	2,677 (38)	1,304 (32)	1,373 (46)
High-flow nasal cannula and/or noninvasive ventilation	1,206 (17)	665 (16)	541 (18)
Invasive mechanical ventilation	1,888 (27)	1,327 (33)	561 (19)
Age (yr), median (IQR)	61 (48–72)	62 (50–73)	59 (45–71)
Sex, *n* (%)			
Male	4,131 (58)	2,387 (58)	1,744 (58)
Female	2,937 (42)	1,698 (42)	1,239 (42)
Race, *n* (%)			
Asian	1,661 (23)	743 (18)	918 (31)
Black or African American	1,597 (23)	1,092 (27)	505 (17)
White	2,969 (42)	1,741 (43)	1,228 (41)
Mixed race/other	751 (11)	474 (12)	277 (9)
Unknown	86 (1)	34 (< 1)	52 (2)
Hispanic ethnicity, *n* (%)	894 (13)	605 (15)	289 (10)
Body mass index (kg/m^2), median (IQR)[a]	29 (25–34)	29 (25–34)	28 (25–33)
Comorbidities, *n* (%)			
Coronary artery disease	876 (12)	495 (12)	381 (13)
Congestive heart failure	605 (9)	316 (8)	289 (10)
Chronic pulmonary disease	580 (8)	342 (8)	238 (8)
Asthma	491 (7)	329 (8)	162 (5)
Chronic kidney disease	919 (13)	584 (14)	335 (11)
Diabetes mellitus	2,415 (34)	1,449 (36)	966 (32)
Liver disease	121 (2)	92 (2)	29 (1)
Hospital medications, *n* (%)			
Antivirals	1,979 (28)	667 (16)	1,312 (44)
Corticosteroids	2,876 (41)	1,029 (25)	1,847 (62)
Hydroxychloroquine	1,779 (25)	1,625 (40)	154 (5)
Immunomodulators	620 (9)	490 (12)	130 (4)
Therapeutic dose anticoagulation	2,154 (31)	1,201 (29)	953 (32)
Admission Sequential Organ Failure Assessment score, median (IQR)[a]	2 (0–4)	3 (1–5)	2 (0–4)
ICU admission, *n* (%)	3,817 (54)	2,196 (54)	1,621 (54)
Hospital mortality, *n* (%)	1,428 (20)	942 (23)	486 (16)

IQR = interquartile range.

[a]Covariate missingness (% missing): Body mass index (23%); Sequential Organ Failure Assessment (37%).

TABLE 2.
Medication Practice Patterns by Pandemic Stage

Pandemic Stage	Cluster Number	Cluster Size	Silhouette Width	Hospital-Level Medication Prescription Proportion				
				Antiviral	Corticosteroids	Hydroxychloroquine	Immunomodulators	Therapeutic Anticoagulation
Early pandemic stage	1	11	0.29	0.35	0.22	0.01	0.04	0.24
	2	12	0.07	0.09	0.38	0.56	0.06	0.44
	3	5	0.13	0.04	0.22	0.74	0.39	0
	4	4	0.46	0.29	0.21	0.14	0.07	0.82
	5	5	0.04	0.30	0.60	0.10	0	0.30
	6	7	0.32	0.09	0.15	0.24	0.03	0.06
	7	7	0.30	0.02	0.11	0.68	0.06	0.09
	8	3	0.31	0.82	0.06	0.12	0.06	0.06
	9	5	0.21	0	0.90	0.72	0.28	0.97
Mid-late pandemic stage	1	28	0.41	0.49	0.74	0.01	0.03	0.12
	2	4	0.58	0	0.92	0.10	0.29	0.96

cluster compared with hospitals in different medication practice clusters (Supplemental Figs. 2 and 3, http://links.lww.com/CCX/A830). Sensitivity analysis using the elbow method was similar (**Supplemental Figs. 4–6**, http://links.lww.com/CCX/A830).

Risk-Adjusted Mortality of Repurposed Medication Phenotypes

During the early pandemic stage, there were 37 hospitals categorized within the experimental practice phenotype with routine use of at least one repurposed medication of interest compared with 22 hospitals within the conservative practice phenotype. There was no difference in risk-adjusted mortality between experimental hospitals and conservative hospitals (OR, 1.16; 95% CI, 0.83–1.63). Similarly, there was no significant difference in risk-adjusted mortality during the mid-late pandemic between the 28 hospitals in cluster 1 and 4 hospitals in cluster 2 (OR, 0.32; 95% CI, 0.05–2.06).

DISCUSSION

In this large, observational, international study, we identified extensive variation in the use of medications repurposed for management of COVID-19 over the first year of the pandemic, particularly during the initial months of the pandemic, with less variation and more uniform evidenced-based practice in the later pandemic stage.

To date, there are limited studies on the variation in use of repurposed medications for management of COVID-19. An online survey of predominantly European intensivists, conducted during the "early pandemic stage" (May 2020), found that 48.9% and 52.4% of respondents felt there was too little evidence to support the use of antivirals or anti-inflammatory therapies for COVID-19 management, respectively (20). Among the most commonly used repurposed medications, they found 36.6% of intensivists used antivirals, 31.5% used corticosteroids, 42.7% used hydroxychloroquine, and 24.8% used immunomodulators prior to May 2020 (20). Another retrospective study found that among 35,000 patients hospitalized with COVID-19 from March 2020 to May 2020, 45.8% received hydroxychloroquine, 21.5% received corticosteroids, and 5.7% received tocilizumab. Our findings expand upon these prior studies through quantification of the hospital-level variation in medication use and through identification of medication patterns throughout the COVID-19 pandemic. As seen by the high median ORs (ranging from 3.09 to 5.95 across medications) and high portion of the variation in use attributed to hospital site alone (ranging from 30% to 52%), hospital of admission was a major driver in use of repurposed medications for COVID-19.

The wide variation in hospital-level use of repurposed medications was most pronounced early in the pandemic with nine medication practice pattern clusters,

suggesting that hospital practice was widely idiosyncratic in the absence of RCTs and evidenced-based guidelines during the initial months of the pandemic. The more uniform medication practice in the mid-late pandemic stage coincides with the arrival of clinical trial results. The antiviral, remdesivir, was the first repurposed medication found to have RCT evidence of clinical benefit, with a reduction in time to clinical improvement, among patients with COVID-19 (7, 8). At the start of the COVID-19 pandemic, use of corticosteroids was controversial due to the known association with increased mortality in influenza and delayed viral clearance in severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus (21). However, the results of the Randomised Evaluation of COVID-19 Therapy RCT later showed a reduction in 28-day mortality among patients with COVID-19 on supplemental oxygen who received dexamethasone (9, 10). In contrast to corticosteroid use, hydroxychloroquine was used early on based on a small nonrandomized trial suggesting reduced COVID-19 viral loads (22), further driven by the intrusion of politics and clinician desperation for effective therapeutics (23). Between June 2020 and July 2020, the results of multiple RCTs showed that hydroxychloroquine use was not associated with mortality benefit or improvement in clinical status compared with usual care (11, 12). Initial trials of immunomodulators for management of COVID-19 did not show a reduction in disease progression, invasive mechanical ventilation, or mortality likely resulting in the decrease in use of immunomodulators seen over time (24–26). However, recent immunomodulator RCTs published in 2021, which have shown reduced progression to invasive mechanical ventilation and death, may not be reflected in our study due to the dates of our data collection (13, 14). While our results showed that there was a statistically significant increase in use of therapeutic dose anticoagulants over time, this was not a clinically significant change. This corresponds with the equivocal evidence surrounding use for therapeutic dose anticoagulants that requires further investigation to determine the optimal approach to mitigating thrombotic complications associated with COVID-19 (27–30). In general, clinical practice changes coincided with emerging evidence.

The results of our study should inform the approach to the next pandemic. The decision to use repurposed medications was based on anecdotal evidence, left to the discretion of the treating clinicians, who were reasonably driven by a sense of "having to try something" in the face of a novel viral illness despite the lack of supporting evidence (23, 31–33). The lack of association between widespread use of repurposed medications and improved mortality underscores the hidden costs of widespread anecdotal medication use, including increased expense, confusion regarding scientific equipoise for randomized trial planning, and potential for adverse events with use of ineffective therapies. Previously designed investigative platforms, such as Randomized Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia and Adaptive COVID-19 Treatment Trial, provided the organizational structure needed to conduct rapid and robust comparative effectiveness studies and RCTs; results of which were rapidly implemented. However, without widespread access to randomized trials, use of unstudied medications could not meaningfully contribute to rigorous evidence generation or a "learning healthcare system" (34). Future efforts to channel the clinical drive to use potentially effective—but unproven—therapeutics for patients in the face of uncertainty into widespread national programs that rapidly enroll patients into rigorous clinical trials are urgently needed for the next pandemic.

Strengths

Strengths of the study include the use of a large, multicenter, global cohort of adult patients hospitalized with COVID-19 throughout the pandemic. The VIRUS registry consists predominantly of the gold standard of data extraction with manual chart review with weekly data quality assessment. Additionally, the use of CLARA was a novel approach to characterize complex medication practice patterns across hospitals and how practice patterns changed over the course of the pandemic.

Limitations

There are several limitations to this study. First, the retrospective, observational study design allows for unmeasured confounders that may influence medication prescription patterns. Second, missing covariate data may not be missing completely at random, which may affect multivariable adjusted associations between fixed effects and medication use. Third, resource constraints, medication availability, and

pandemic case volume were not assessed, which may further contribute to hospital-level repurposed medication prescription practice. Fourth, unsupervised cluster analysis was limited by smaller hospital and patient cohorts in the mid-late pandemic stage compared with the early pandemic stage, which may have been affected by variable pandemic case volume and site data entry. Fifth, exploratory analysis of risk-adjusted mortality between different medication practice phenotypes may have been underpowered and requires further investigation.

CONCLUSIONS

We identified wide variation in the hospital-level use of repurposed medications early in the COVID-19 pandemic, which became more uniform in the mid-late pandemic stage with the arrival of clinical trial evidence. Repurposed medication practice during the mid-late pandemic stage was more evidenced-based with increased use of antivirals and corticosteroids, reduced use of hydroxychloroquine and immunomodulators, and relatively unchanged use of therapeutic dose anticoagulants. The wide variation in repurposed medication use and delay to equitable and evidenced-based practice highlights the need to develop platforms designed for rapid activation and implementation of comparative effectiveness studies and RCTs at the start of the next pandemic.

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REFERENCES

1. Walkey AJ, Kumar VK, Harhay MO, et al: The Viral Infection and Respiratory Illness Universal Study (VIRUS): An international registry of coronavirus 2019-related critical illness. *Crit Care Explor* 2020; 2:e0113
2. Walkey AJ, Sheldrick RC, Kashyap R, et al: Guiding principles for the conduct of observational critical care research for coronavirus disease 2019 pandemics and beyond: The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2020; 48:e1038–e1044
3. Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42:377–381
4. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208

5. Domecq JP, Lal A, Sheldrick CR, et al; Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group: Outcomes of patients with coronavirus disease 2019 receiving organ support therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. *Crit Care Med* 2021; 49:437–448
6. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
7. Kadri SS, Demirkale CY, Sun J, et al: Real-world inpatient use of medications repurposed for coronavirus disease 2019 in United States hospitals, March–May 2020. *Open Forum Infect Dis* 2021; 8:1–6
8. Wang Y, Zhang D, Du G, et al: Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; 395:1569–1578
9. Horby P, Lim WS, Emberson J, et al: Effect of dexamethasone in hospitalized patients with COVID-19 – preliminary report. *medRxiv* Preprint posted online June 22, 2020. doi: 10.1101/2020.06.22.20137273
10. Horby P, Shen Lim W, Emberson JR, et al; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021; 384:693–704
11. Horby P, Mafham M, Linsell L, et al; The RECOVERY Collaborative Group: Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020; 383:2030–2040
12. Cavalcanti AB, Zampieri FG, Rosa RG, et al; Coalition Covid-19 Brazil I Investigators: Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *N Engl J Med* 2020; 383:2041–2052
13. Gordon AC, Mouncey PR, Al-Beidh F, et al: Interleukin-6 receptor antagonists in critically ill patients with Covid-19. *N Engl J Med* 2021; 384:1491–1502
14. Salama C, Han J, Yau L, et al: Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med* 2021; 384:20–30
15. Merlo J, Chaix B, Ohlsson H, et al: A brief conceptual tutorial of multilevel analysis in social epidemiology: Using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006; 60:290–297
16. Kaufman L, Rousseeuw PJ: Finding Groups in Data: An Introduction to Cluster Analysis. New York, Wiley, 1990, pp 126–163
17. Batool F, Hennig C: Clustering with the average silhouette width. *Comput Stat Data Anal* 2021; 158:107190
18. Kodinariya TM, Makwana PR: Review on determining number of cluster in K-means clustering. *Int J Adv Res Comput Sci Manag Stud* 2013; 1:2321–7782
19. Jakobsen JC, Gluud C, Wetterslev J, et al: When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017; 17:162
20. Azoulay E, de Waele J, Ferrer R, et al: International variation in the management of severe COVID-19 patients. *Crit Care* 2020; 24:486
21. Yang JW, Yang L, Luo RG, et al: Corticosteroid administration for viral pneumonia: COVID-19 and beyond. *Clin Microbiol Infect* 2020; 26:1171–1177
22. Gautret P, Lagier JC, Parola P, et al: Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020; 56:105949
23. Saag MS: Misguided use of hydroxychloroquine for COVID-19: The infusion of politics into science. *JAMA* 2020; 324:2161–2162
24. Stone JH, Frigault MJ, Serling-Boyd NJ, et al; BACC Bay Tocilizumab Trial Investigators: Efficacy of tocilizumab in patients hospitalized with Covid-19. *N Engl J Med* 2020; 383:2333–2344
25. Hermine O, Mariette X, Tharaux PL, et al; CORIMUNO-19 Collaborative Group: Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. *JAMA Intern Med* 2021; 181:32–40
26. Salvarani C, Dolci G, Massari M, et al; RCT-TCZ-COVID-19 Study Group: Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. *JAMA Intern Med* 2021; 181:24–31
27. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al: Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). *Thromb Res* 2020; 196:359–366
28. Zarychanski R: Therapeutic anticoagulation in critically ill patients with Covid-19 – preliminary report. *medRxiv* Published online January 1, 2021. doi: 10.1101/2021.03.10.21252749
29. Lopes RD, de Barros E Silva PGM, Furtado RHM, et al; ACTION Coalition COVID-19 Brazil IV Investigators: Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): An open-label, multicentre, randomised, controlled trial. *Lancet* 2021; 397:2253–2263
30. Talasaz AH, Sadeghipour P, Kakavand H, et al: Recent randomized trials of antithrombotic therapy for patients with COVID-19: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2021; 77:1903–1921
31. Baden LR, Rubin EJ: Covid-19 - the search for effective therapy. *N Engl J Med* 2020; 382:1851–1852
32. Friedrich S, Friede T: Causal inference methods for small non-randomized studies: Methods and an application in COVID-19. *Contemp Clin Trials* 2020; 99:106213
33. Serpa Neto A, Hodgson C: Will evidence-based medicine survive the COVID-19 pandemic? *Ann Am Thorac Soc* 2020; 17:1060–1061
34. Institute of Medicine (US) Roundtable on Evidence-Based Medicine, Olsen L, Aisner D, McGinnis JM, eds. The Learning Healthcare System: Workshop Summary. Washington (DC), National Academies Press (US); 2007