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Increased laboratory value normalization and survival in an international cohort of hospitalized patients with SARS-CoV-2: a temporal analysis of the pandemic

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KEY POINTS:

QUESTION: Have outcomes for hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) improved over time?

FINDINGS: In this cohort study of 83,178 patients hospitalized with SARS-CoV-2, 28-day mortality rates stratified by predicted low, medium, or high mortality risk using baseline covariates at admission all decreased over time. Patients admitted from July 2020 to January 2021 also exhibited faster improvement rates in laboratory values than patients admitted in March to June of 2020.

MEANING: Despite presenting with similar clinical profiles and laboratory values, patients experienced faster improvement and decreased mortality in later periods of the pandemic. This suggests that changes in medical management and improved resource utilization played a role in reducing mortality over time.

ABSTRACT:

OBJECTIVE: To assess changes in international mortality rates and laboratory recovery rates during hospitalization for patients hospitalized with SARS-CoV-2 between the first and second waves of the COVID-19 pandemic.

DESIGN, SETTING, AND PARTICIPANTS: This is a retrospective cohort study of 83,178 hospitalized patients admitted before or after polymerase chain reaction-confirmed SARS-CoV-2 infection within the Consortium for Clinical Characterization of COVID-19 by EHR (4CE), an international multi-healthcare system collaborative of 288 hospitals in the United States (US) and Europe.

PRIMARY and SECONDARY OUTCOMES MEASURES: The primary outcome was all-cause mortality rate within 28 days after hospitalization stratified by predicted low, medium, and high

mortality risk at baseline. The secondary outcome was the average rate of change in laboratory values during the first week of hospitalization.

RESULTS: Baseline Charlson comorbidity index and laboratory values at admission were not significantly different between the first and second waves. The improvement in laboratory values over time was faster in the second wave compared to the first. The average CRP rate of change was –4.72 vs. –4.14 mg/dL per day (p=0.05). The mortality rates within each risk category significantly decreased over time, with the most substantial decrease in the high-risk group (42.3% in March–April 2020 vs 30.8% in November 2020–January 2021, p<0.001) and a moderate decrease in the intermediate-risk group (21.5% in March–April 2020 vs. 14.3% in November 2020–January 2021, p<0.001).

CONCLUSIONS: Admission profiles of patients hospitalized with SARS-CoV-2 infection did not differ greatly between the first and second waves of the pandemic, but there were notable differences in laboratory improvement rates during hospitalization. Mortality risks among patients with similar risk profiles decreased over the course of the pandemic. The improvement in laboratory values and mortality risk was consistent across multiple countries.

STRENGTHS AND LIMITATIONS:

- Our federated approach avoided privacy concerns and regulatory barriers common in multicentre studies while facilitating timely international analyses of 83,178 patients from five countries.
- Our common data model along with iterative quality control efforts provide assurance on harmonized data quality.
- The current study may include patients who were either hospitalized due to COVID-19 or had a positive test for SARS-CoV-2 when admitted for an unrelated medical condition.
- For most 4CE participating healthcare systems, we were unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality among inpatients occurs in the hospital and many discharged patients have post-discharge follow-up visits, which allow us to capture 28-day mortality reasonably well.

INTRODUCTION

Mortality rates among hospitalized patients with SARS-CoV-2 infection have decreased over the course of the COVID-19 pandemic [1–3]. It has been hypothesized that this may reflect a higher proportion of younger patients being hospitalized later in the pandemic, but a recently published study reported significant decreases in mortality after stratification by age group [4,5]. A variety of factors are likely responsible, including, but not limited to, improvements in clinical management, resource allocation, and earlier detection of disease [6–12]. There is limited evidence to shed light on these hypotheses; few studies have examined improvements of in-hospital recovery and outcomes over the course of the pandemic. In this international multi-healthcare system retrospective cohort study, we leveraged electronic health records (EHR) data from hospitalized COVID-19 patients to examine temporal shifts in (1) the rate of change for laboratory values towards normal during hospitalization and (2) mortality rates stratified by baseline mortality risk.

METHODS

Individual-level EHR data on hospitalized COVID-19 patients from 18 healthcare systems of the 4CE consortium [13] were extracted and harmonized for this study. Supplementary Table 1 reports further metadata on the participating healthcare systems, which represent 288 hospitals across five countries: France, Germany, Italy, Spain, and the US. Each healthcare system ran the analyses locally and reported summary results to the central institution for federated analyses. Institutional review board approval was obtained at each healthcare system. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [14].

Cohort Identification and Data Collection

Our study included 83,178 patients admitted 7 days before to 14 days after the date of their first positive reverse transcription-polymerase chain reaction SARS-CoV-2 test result recorded in their EHR. We included patients admitted between March 1, 2020 and January 31, 2021 with follow-up data up to June 2021.

We obtained patient-level data on demographics including age groups (18-25, 26-49, 50-69, 70-80, 80+), sex, and race; laboratory test values during hospitalization; International Classification of Disease (ICD) codes, date of discharge, and mortality information. Only US sites reported race. We calculated the Charlson comorbidity index (CCI) based on ICD codes [15–17]. We focused on ten laboratory tests: C-reactive protein (CRP), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, D-dimer, white blood cell count, lymphocyte count, and neutrophil count [8,18–22]. A schematic of our workflow is presented in eFigure 1.

Primary and Secondary Outcomes

We defined all-cause mortality up to 28 days after the admission date as the primary outcome and excluded patients who died on the day of admission in the survival analysis. Each 4CE healthcare system used local criteria to identify in-hospital mortality. We defined laboratory test values during hospitalization as secondary outcomes.

Statistical Analysis

To assess temporal changes over the course of the pandemic, we performed stratified analyses by every two calendar months and between two waves of the pandemic, wherein we defined the first wave as from March 1 to June 30, 2020 and the second wave as from July 1, 2020 to January 31, 2021.

We summarized demographic characteristics, the average CCI at admission, hospitalization duration, and absolute mortality risk over time. Since the VA population has a distinct demographic composition, we reported demographic summaries excluding the VA. We further compared the distributions of admission laboratory values between the two waves.

To summarize the laboratory trajectories during hospitalization, we fit log-linear mixed effects models to the longitudinal laboratory data with cubic splines for time since admission, where we used three knots at days 3, 7, and 17 in the fixed effects to capture nonlinear trends. Since laboratory trajectories may vary by how quickly patients recover, we stratified the trajectory analysis by the hospitalization duration ≤1 week, 1-2 weeks, and 2+ weeks. For each laboratory test, we summarized the *average daily rate of change during the first week of hospitalization* in the first and second waves, denoted by R_1 and R_2. The laboratory trajectory analyses only included data from the US, France, and Spain since few patients from the Germany and Italy sites had repeated laboratory tests.

To study temporal changes in mortality risks, we fit LASSO penalized Cox proportional hazard models for mortality using baseline covariates adjusted for calendar time of the admission date [23,24]. We considered three sets of covariates: (1) age, sex, and race; (2) the ten laboratory tests; and (3) CCI. We modeled the calendar time effect using a cubic spline with knots every 2 weeks. We performed a $\log_e$-transformation to D-dimer, CRP, and ALT due to the skewness in their distributions. Due to the high correlation between ALT and AST, we include AST to ALT ratio (AST/ALT) and $\log_e$ALT as measures of liver function [25,26] instead of $\log_e$AST and $\log_e$ALT. We imputed missing baseline laboratory measures and CCI via the multivariate imputation by chained equation method and averaged over five imputed sets [27]. The mortality analyses excluded Italy since a very small number of deaths occured after April 2020 in the participating healthcare systems.

From a fitted penalized Cox model, we obtained a mortality risk score for each patient given their baseline covariates. We calculated the area under the receiver operating characteristic curve (AUC) of the risk score for predicting 28-day mortality [28]. We classified patients into three mortality risk groups according to their risk score: high risk if score > c_{high}, medium risk if score ∈ (c_{low}, c_{high}), and low risk if score ≤ c_{low}. We chose c_{low} and c_{high} to attain a sensitivity of 85% (c_{low}) and a specificity of 85% (c_{high}) for predicting 28-day mortality, which ensures a good separation between the low-risk and high-risk categories. Stratifying by the calendar time window of the admission date, we calculated the AUC of the risk model, the proportions of patients belonging to each risk category, and their corresponding mortality risks.

The accuracy parameters were estimated via ten-fold cross-validation to correct for overfitting [29]. We used bootstrap to estimate standard errors [30].

Patient-level analyses were performed within each 4CE healthcare system to obtain site-specific results. We integrate results from all sites using fixed effects meta-analysis. Since the number of hospitalized patients had a different temporal trend across healthcare systems and across countries, we assigned the same weight across different calendar months for each healthcare system to facilitate effective comparisons between waves. All statistical analyses were performed using R software version 4.0.2.

RESULTS

Characteristics of the Study Cohort

The majority of patients were hospitalized March–April 2020 and November 2020 to January 2021 (Figure 1). The most prevalent age group at any time was ages 50–69. In the US—excluding VA patients which are summarized in eFigure 2—the prevalence of patients who were White increased (49.1% in March–April 2020 to 64.1% in November 2020–January 2021, $p<0.001$), while the prevalence of patients who were Black decreased (30.0% in March–April 2020 to 17.4% in November 2020–January 2021, $p<0.001$). The average CCI at admission remained relatively constant across time. The mortality rate decreased from 20.7% in March–April 2020 to 11.9% in July–August 2020 ($p<0.001$), then increased slightly to 12.4% in November 2020–January 2021 ($p<0.001$). The temporal shifts in the number of hospitalized patients, demographics, CCI, and mortality rate were generally consistent across countries (eFigure 2).

As shown in Figure 2, CRP, creatinine, and D-dimer values at admission were lower in the first wave compared to the second but these differences were not statistically significant. The between-wave CRP mean difference was higher for France (18.5 mg/dL; 95% CI, 16.5-20.5) and Spain (8.4 mg/dL; 95% CI, 4.8-12.0) compared to the US (7.5 mg/dL; 95% CI, 6.1-8.8) and Germany (6.7 mg/dL; 95% CI, –2.5-16.1) (eFigure 3).

Change in Laboratory Trajectory During Hospitalization

Patients' laboratory trajectories during hospitalization improved faster in the second wave compared to the first (Figure 3). CRP decreased more rapidly (R_1= –4.14 vs. R_2= –4.72 mg/dL per day, p=0.05), while D-dimer increased substantially faster during the first wave but did not change appreciably during the second (R_1=21.01 vs. R_2=1.25 ng/dL per day, p<0.001).

Hospitalization duration decreased, with 53.4% of patients discharged within 1 week in the second wave compared to 49.2% in the first (p<0.001). Patients hospitalized for longer generally had worse laboratory profiles compared to those with shorter stays. The average day-3 CRP among those hospitalized for ≤ 1week and 2+ weeks was 41.68 and 63.64 mg/dL (p<0.001) during the first wave and 27.33 and 43.52 mg/dL (p<0.001) during the second wave. The between-wave difference in the rate of decline, Δ_R=R_1-R_2, also varied by the duration of hospitalization. For CRP, Δ_R was 1.01 (p<0.001), 2.04 (p<0.001) and 0.95 (p=0.001) mg/dL per day among those hospitalized for ≤ 1, 1-2, and 2+ weeks. For creatinine and D-dimer, Δ_R had similar patterns but were not statistically significant.

The improvement in laboratory values was more pronounced in the US than in France and Spain (eFigure 4). For CRP, Δ_R = 1.07 mg/dL per day (95% CI, 0.86-1.28) in the US, which is significantly higher than that of France (–0.69 mg/dL per day, 95% CI, –1.08- 2.92), and Spain (–0.3 mg/dL per day, 95%CI,–0.79-0.19). The reduction in hospitalization duration varied greatly between countries. The higher patients discharged within 1 week increased in the second wave compared to the first in the US (53.4% vs 61.1%, p<0.001), Italy (2.5% vs 14.9%, p<0.001), Germany (32.7% vs 48.6%, p<0.001), and Spain (57.1% vs 62.3%, p<0.001), but decreased in France (46.1% vs 42.4%, p<0.001).

Temporal Changes in Mortality Risk

The factors significantly associated with increased risk of mortality were older age, male sex, CCI, lower albumin and lymphocyte count, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT at baseline (Figure 4). The hazard ratios of these risk factors did not vary significantly between countries (eFigure 5).

Over the course of the pandemic, the models' predictive capabilities did not significantly change with AUC ranging from 0.752 to 0.787; the temporal patterns were similar across countries (eFigure 6).

The proportion of high-risk patients decreased from March-April 2020 to July-August 2020 but gradually increased from September 2020 to January 2021 (Figure 5). However, the mortality rates within each risk category decreased over calendar time, with the decrease from March–April 2020 to November 2020–January 2021 most substantial in the high-risk category (47.1% vs. 30.8%, p <0.001), moderate in the intermediate-risk (25.6% vs. 14.8%, p <0.001), and the low-risk (9.5% vs 4.7%, p<0.001) categories. From March–April 2020 to November 2020–January 2021, the US had a more consistent decrease over time while France and Spain decreased from March–April 2020 to July–August 2020 but plateaued afterwards (eFigure 7). In the high-risk category, the decrease in mortality risk from March–April 2020 to July–August 2020 was the highest in Spain (42.7% vs 25.0%, p=0.002), followed by the US (50.0% vs 38.4%, p<0.001), and France (40.1% vs. 31.7%, p=0.11). By November 2020–January 2021, the mortality risk further decreased to 29.5% (95% CI, 28.3-30.7) in the US, but slightly increased to 34.9% (95% CI, 31.7-38.0) in France and 28.6% (95% CI, 22.9-34.3) in Spain.

DISCUSSION

In this large, international, multi-healthcare system retrospective cohort study, we found that older age, male sex, higher CCI, low albumin and lymphocyte count values, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT were significantly associated with higher mortality risk across all represented countries. While our findings corroborate prior observations that male sex, advanced age, and comorbidities are major risk factors for mortality, we found interesting associations of higher AST/ALT, ALT, and bilirubin with mortality. While derangements in liver function tests are well described in prior studies of patients with COVID-19, the patterns of liver dysfunction associated with worse outcomes are inconsistent [31,32]. Furthermore, these studies tend to be derived from single-center studies which likely introduce significant sources of bias. In particular, our observation of a combination of elevated markers of cholestatic liver function (bilirubin, AST/ALT ratio) and

inflammatory markers and cell counts suggest cholestatic liver dysfunction may be common in patients with COVID-19, as is observed in patients who are critically ill [33–35]. Furthermore, emerging COVID-19 post-mortem studies have suggested that SARS-CoV-2 may directly infect hepatocytes and lead to altered bile duct morphology, reinforcing the possible role of viral-induced cholestatic hepatitis in severe COVID-19 [35]. Alternatively, medication-related liver injury could certainly contribute to liver dysfunction. Future investigations utilizing patient-level data validated by thorough chart review is warranted to better define these associations.

Overall, we observed greater improvements in positive and negative acute phase reactants and markers of organ function (e.g., creatinine, ALT, and AST) in the second wave compared to the first, which suggests that systemic inflammation and multiorgan dysfunction all improved faster in the second wave. Interestingly, we observed a greater improvement in CRP, ALT, AST, and creatinine in the second wave in patients with longer hospitalizations; while this may be reflective of a sicker patient population, this could be due to time-dependent (i.e., survivor) bias [36]. Alternatively, there may have been increased corticosteroid use in patients with severe COVID-19 in the second wave following preliminary results of the RECOVERY trial, which may have improved inflammatory markers and mortality [12,37][38]. In addition, there may have been increased remdesivir in combination with dexamethasone between the first and second waves that may confound these associations [11,37]. Further studies are warranted to investigate the alteration of biochemical trajectories of dexamethasone with remdesivir in contrast to dexamethasone or remdesivir monotherapy [39]. It is also unclear why we observed between-country differences in the between-wave CRP trajectories, whereas Spain and France had blunted improvement rates; this could certainly be due to differential clinical management across countries.

One explanation for the blunted D-dimer trajectories in the second wave compared to the first is increased prophylactic anticoagulation use after the release of International Society on Thrombosis and Haemostasis guidelines in May and September 2020, which recommended prophylactic anticoagulation with low-molecular-weight heparin in all hospitalized patients with COVID-19 who had no anticoagulation contraindications [40]. This may have reduced the higher incidence of thrombotic events observed in the first wave, which could be associated with high

D-dimer levels. Furthermore, as D-dimer is often correlated with disease severity and systemic inflammation, increased glucocorticoid use in patients with severe disease could blunt increases in D-dimer [41–44].

Despite few changes in patient demographic and clinical profiles at admission, stratified mortality rates decreased significantly, and patient laboratory profiles displayed faster physiological recovery. Therefore, our findings cannot be entirely explained by a less vulnerable and severely ill cohort of patients admitted in the second wave [5,45–47]. Given that no new major effective pharmacologic therapies were introduced between the first and second waves, new pharmacologic therapies cannot completely explain these observations[48–57]. Alternatively, this may be attributed to changes in indications for admission, inpatient management strategies, and structural characteristics in the latter stages of the pandemic. For example, continuous positive airway pressure reduces the need for mechanical ventilation, and high positive end-expiratory pressure and prone positioning optimizes oxygenation [10,58,59]. Further, negative trial data for hydroxychloroquine, azithromycin, and other pharmacologic agents may have led to reduced usage of these drugs and reduced drug-related adverse effects over the course of the pandemic [40,55,60–62]. Although there is certainly variability in how each healthcare system—and each country—adopted new inpatient management strategies, our results nonetheless suggest that valuable experience was gained to improve patient care. Structurally, hospitals may also have benefited from improved resource allocation strategies and smaller surges in hospitalizations at any given time [63]. Further investigations into the potential explanations are warranted as this study was not designed to infer the specific reasons for this improvement.

Although cross-country and cross-healthcare-system heterogeneities exist in demographics and laboratory distributions, we observed concordant improvement patterns in both laboratory recovery during hospitalization and mortality risk over time across different countries. However, the admission profile-adjusted temporal change in mortality risk over calendar months differed slightly between the US and Europe (Spain and France). In addition to an increase in hospitalization duration in the latter half of the pandemic in France, in Spain and France the mortality risk plateaued overall and actually increased in the high-risk group. Further

investigation into these between-country differences in mortality using chart review and other validation steps is warranted.

Study Strengths and Limitations

This study has several limitations. First, similar to other EHR-based studies, the current study may include patients who were either hospitalized due to COVID-19 or had a positive test for SARS-CoV-2 when admitted for an unrelated medical condition. Second, for most 4CE participating healthcare systems, we were unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality among inpatients occurs in the hospital and many discharged patients have post-discharge follow-up visits, which allow us to capture 28-day mortality reasonably well. Our study is at risk for time-dependent bias given that we did not investigate the exact timing of a positive SARS-CoV-2 test relative to admission. This may also be the case for our results stratified by duration of hospitalization. Future analyses that account for medication administration and the subsequent effect on inflammatory markers and creatinine are necessary to infer why these outcomes improved in the second wave.

Our federated approach avoided privacy concerns and regulatory barriers common in multicentre studies while facilitating timely international analyses of 83,178 patients from five countries. Our common data model along with iterative quality control efforts provide assurance on harmonized data quality.

CONCLUSION

Patients' admission profiles did not differ substantially between waves, but there were notable differences in laboratory recovery rates and mortality in the second wave compared to the first.

ETHICS STATEMENT

All study sites were responsible for and obtained ethics approval, as needed, from the appropriate ethics committee at their institution. IRB protocols were reviewed and approved at APHP (IRB00011591, Project CSE-20-29_ClinicalCOVID), Bordeaux University Hospital (Registration #CHUBX2020RE0253), ICSM (Protocol #2518 CE), Mass General Brigham

(IRB#2020P001483), Northwestern University (IRB# STU00212845), University of Kansas (STUDY00146505), University of Freiburg (Application #255/20, Process #210587), and at VA North Atlantic, Southwest, Midwest, Continental, and Pacific (IRB # 3310-x).

The research was determined to be exempt at Hospital Universitario 12 de Octubre (Protocol #20/403), University of Michigan (IRB# HUM00184357), Beth Israel Deaconess Medical Center (IRB# 2020P000565), University of Pittsburgh (STUDY20070095), and University of Pennsylvania (IRB#842813). University of California Los Angeles determined that this study does not need IRB approval because research using limited data sets does not constitute human subjects research.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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DATA SHARING STATEMENT

Only de-identified aggregate data was provided by sites for this study. All aggregate data used in this study are available for download at www.covidclinical.net.

COMPETING INTEREST STATEMENT

There are no competing interests to report.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting, or dissemination plans of the research.

FIGURES and TABLES

Figure 1: Demographic shifts. For demographics variables, we set male sex, age 50-69, and White race as reference groups.

Figure 2: Distribution of laboratory values at admission.

Figure 3: Patient-level laboratory recovery rate.

Figure 4. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

Figure 5. Risk model results w/event rate information and risk stratification.

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Figure 1: Demographic shifts. For demographics variables, we set male sex, age 50-69, and White race as reference groups.

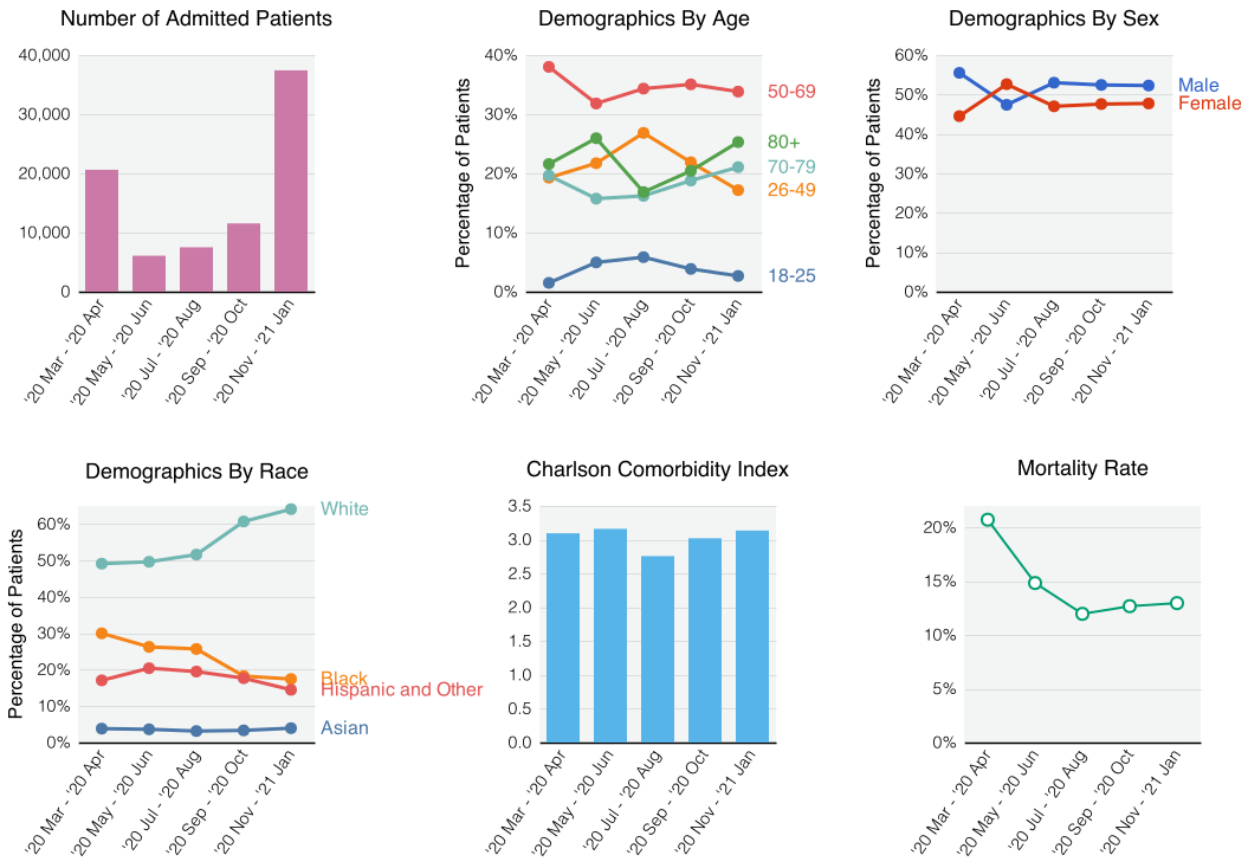


Figure 2: Distribution of laboratory values at admission.

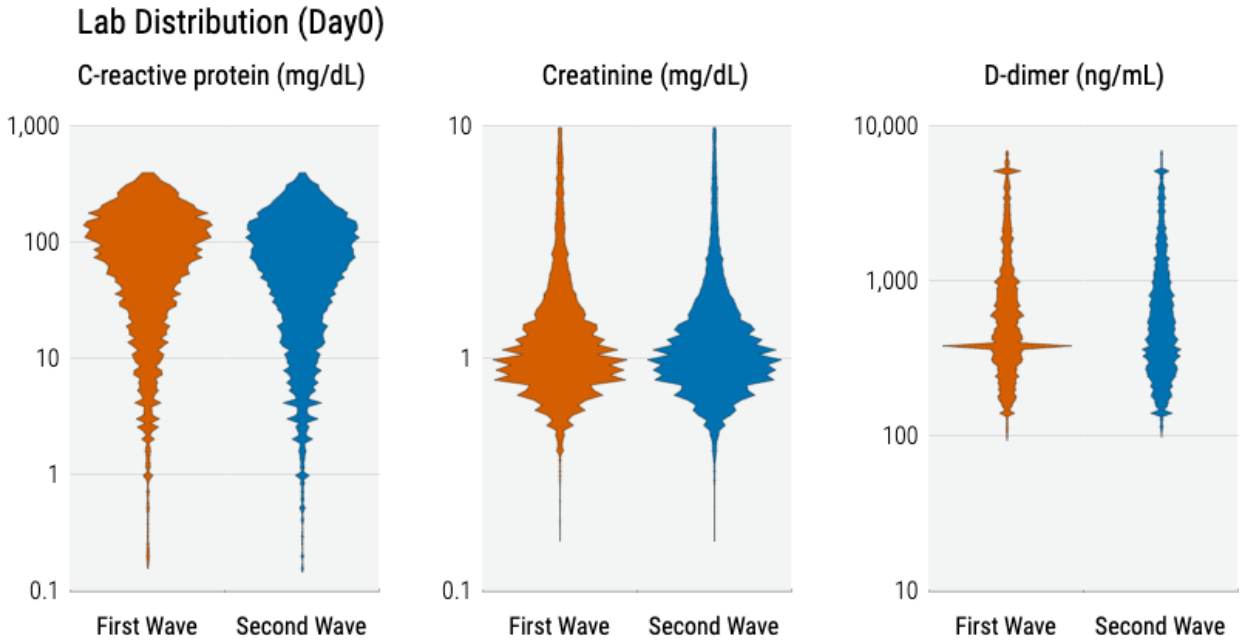


Figure 3: Patient-level laboratory recovery rate.

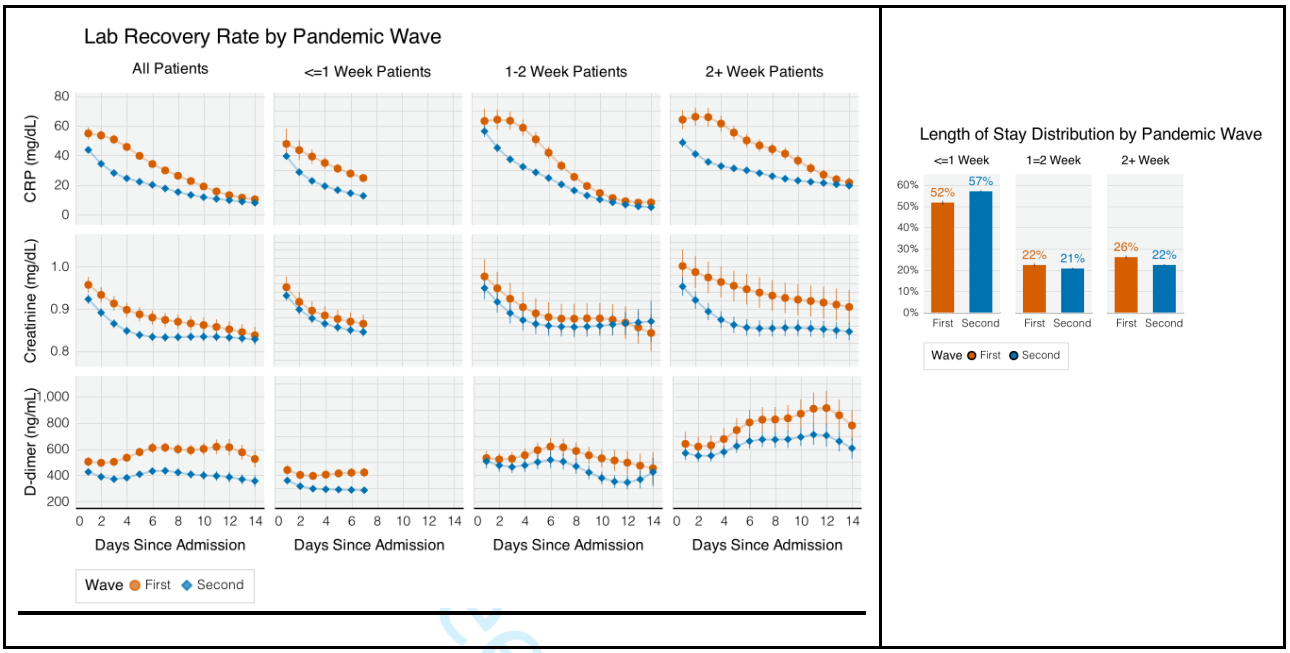


Figure 4. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy)

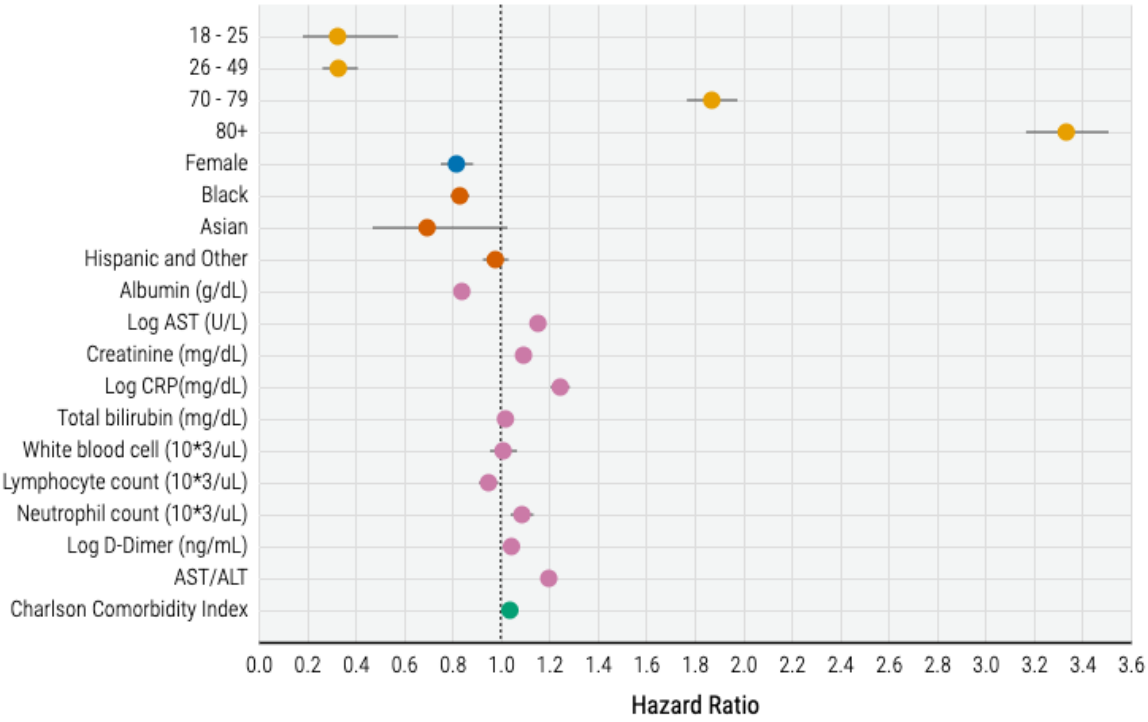
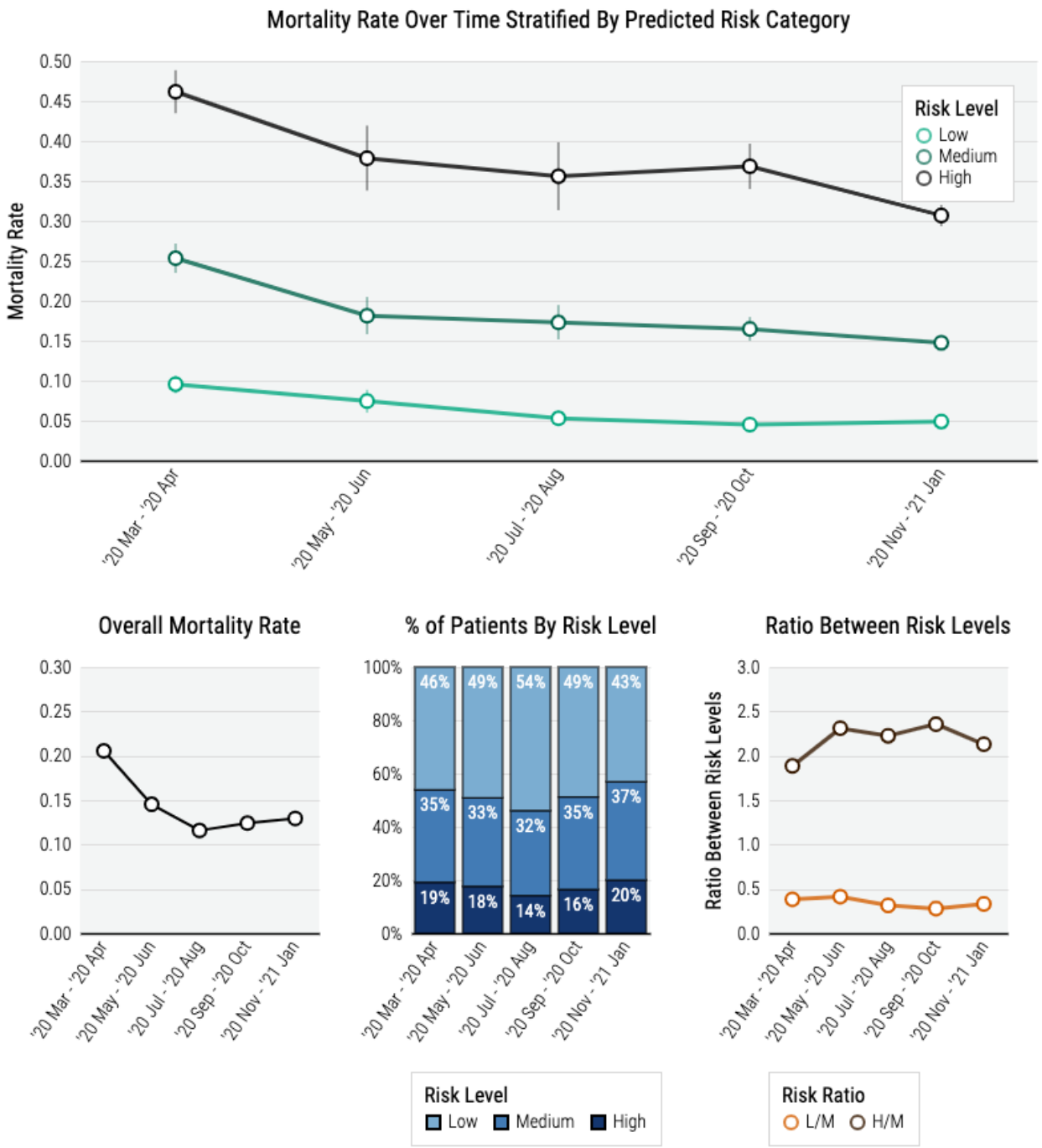


Figure 5: Risk model results w/event rate information and risk stratification.



SUPPLEMENTARY FIGURES

Supplementary eTable 1: Participating hospitals.

Supplementary eFigure 1: Schematic of the federated EHR-based study involving healthcare systems from five countries.

Supplementary eFigure 2: Country-level demographic shifts.

Supplementary eFigure 3: Country-level Distribution of laboratory values at admission.

Supplementary eFigure 4: Patient-level laboratory recovery rate. (a) country-level changes in the recovery rates of laboratory measures (excluding Germany and Italy due to the small number of patients with longitudinal laboratory measurements available); (b) distribution of length of hospital stay among patients admitted in the first wave and in the second wave.

Supplementary eFigure 5: Country-level hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

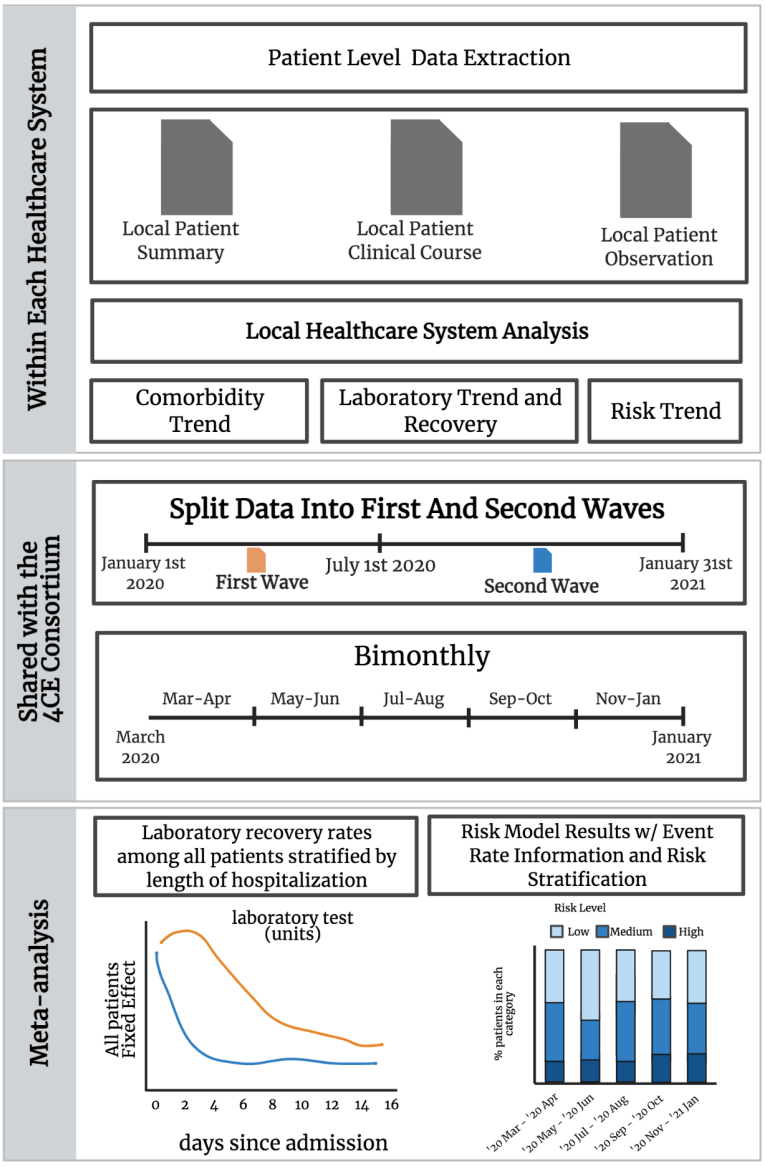
Supplementary eFigure 6. AUC of the Cox regression model for mortality risk prediction (excluding Italy).

Supplementary eFigure 7: Country-level risk model results w/ event rate information and risk stratification (excluding Italy).

eTable 1: Participating healthcare systems.The 170 US Veterans Affairs (VA) hospitals were grouped into 5 regional healthcare systems [1].

Healthcare system	Acronym	Country	City	Hospitals	Beds	Inpatient discharges/ year
Assistance Publique - Hôpitaux de Paris	APHP	France	Paris	39	20 098	1 375 538
Beth Israel Deaconess Medical Center	BIDMC	USA	Boston, MA	1	673	40 752
Bordeaux University Hospital	FRBDX	France	Bordeaux	3	2 676	130 033
Hospital Universitario 12 de Octubre	H12O	Spain	Madrid	1	1 256	45 035
ICSM Hospitals	ICSM	Italy	Pavia/Milan/Lumezzane/Brescia	3	775	12 344
Mass General Brigham (Partners Healthcare)	MGB	USA	Boston, MA	10	3 418	163 521
Northwestern University	NWU	USA	Chicago, IL	10	2 234	103 279
University of California, LA	UCLA	USA	Los Angeles, CA	2	786	40 526
University of Kansas Medical Center	KUMC	USA	Kansas City, KS	1	794	54 659
University of Freiburg, Medical Center	UKFR	Germany	Freiburg	1	1 660	71 500
University of Michigan	UMICH	USA	Ann Arbor, MI	3	1000	49 008
University of Pennsylvania	UPENN	USA	Philadelphia, PA	5	2 469	118 188
University of Pittsburgh	UPITT	USA	Pittsburgh, PA	39	8 085	369 300
VA North Atlantic	VA1	USA		49	3 594	151 075
VA Southwest	VA2	USA		29	3 115	156 315
VA Midwest	VA3	USA		39	2 686	145 468
VA Continental	VA4	USA		24	2 110	113 260
VA Pacific	VA5	USA		29	2 296	114 569
			Total	288	59 725	3 254 370

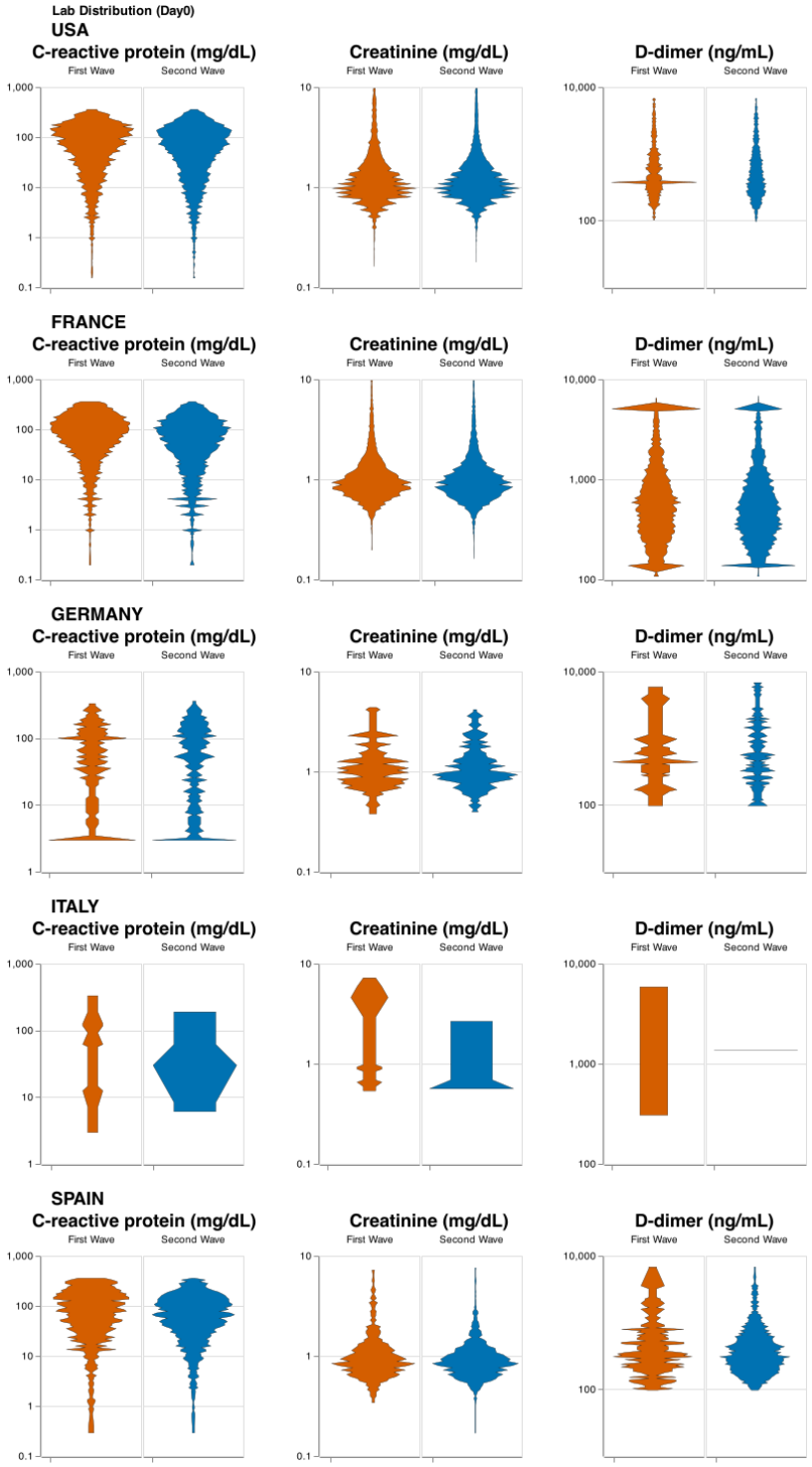
eFigure 1.Schematic of the federated EHR-based study involving healthcare systems from five countries. (created with BioRender.com)



Remark: The hospitalization rate over time tends to differ across regions and across countries, in part due to heterogeneity in a wide range of regional factors including community morbidity and local social distancing policy. This results in different relative sample sizes across healthcare centers over time. To ensure that the temporal trends in clinical presentations summarized via meta-analysis combining all healthcare centers are not driven by the temporal change in the relative sample sizes, we used the same weight for each healthcare center across different calendar months.

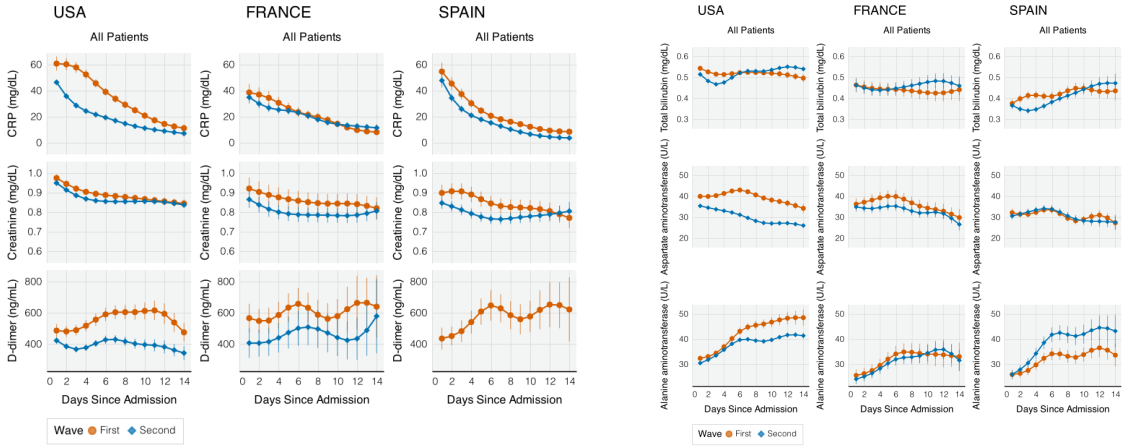
eFigure 2.Country-level demographic shifts.

eFigure 3. Country-level Distribution of laboratory values at admission. The Italy site had a relatively low percentage of patients with laboratory measurements which may have led to less precise estimates in these laboratory changes.

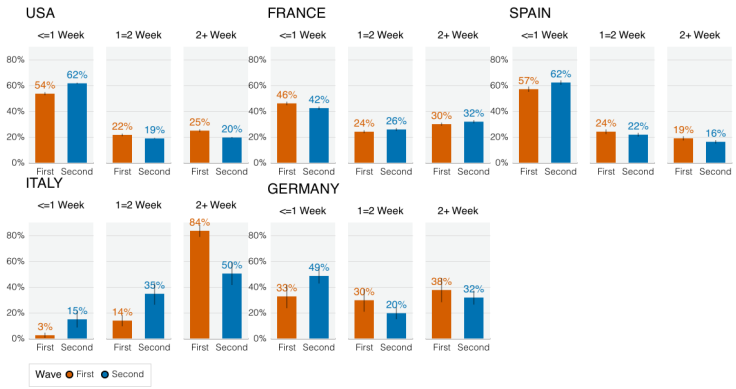


eFigure 4. Patient-level laboratory recovery rate. (a) country-level changes in the recovery rates of laboratory measures (excluding Germany and Italy due to the small number of patients with longitudinal laboratory measurements available); (b) distribution of length of hospital stay among patients admitted in the first wave and in the second wave

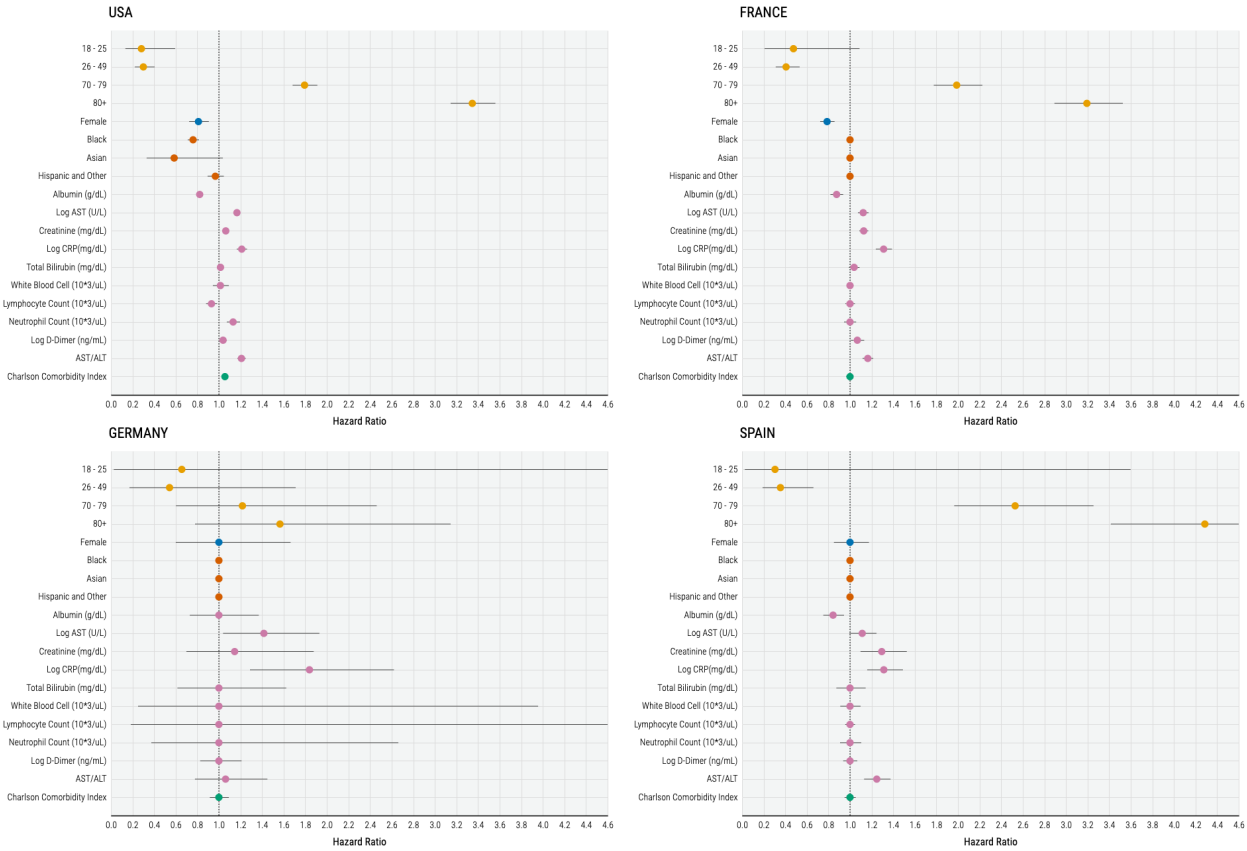
(a) country-level changes in the recovery rates of laboratory measures



(b) Distribution of length of hospital stay among patients admitted in the first wave and in the second wave

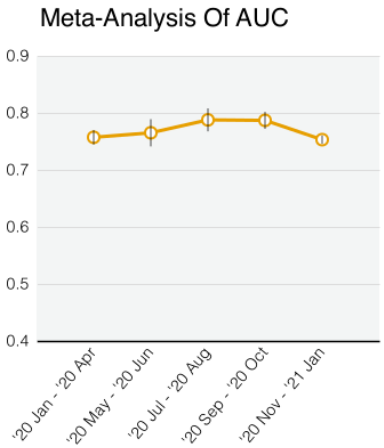


eFigure 5. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

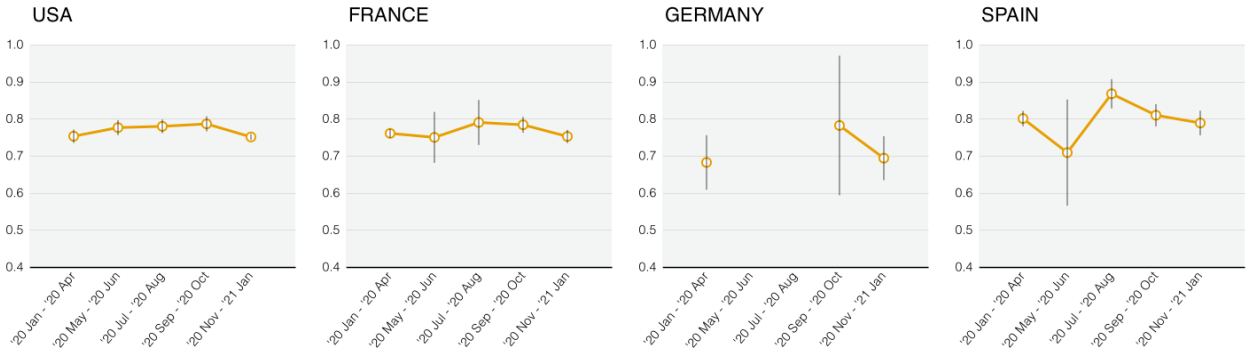

USA
FRANCE
GERMANY
SPAIN
18 - 25
26 - 49
70 - 79
80+
Female
Black
Asian
Hispanic and Other
Albumin (g/dL)
Log AST (U/L)
Creatinine (mg/dL)
Log CRP(mg/dL)
Total Bilirubin (mg/dL)
White Blood Cell (10*3/uL)
Lymphocyte Count (10*3/uL)
Neutrophil Count (10*3/uL)
Log D-Dimer (ng/mL)
AST/ALT
Charlson Comorbidity Index
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6
Hazard Ratio

eFigure 6. AUC of the Cox regression model for mortality risk prediction (excluding Italy).

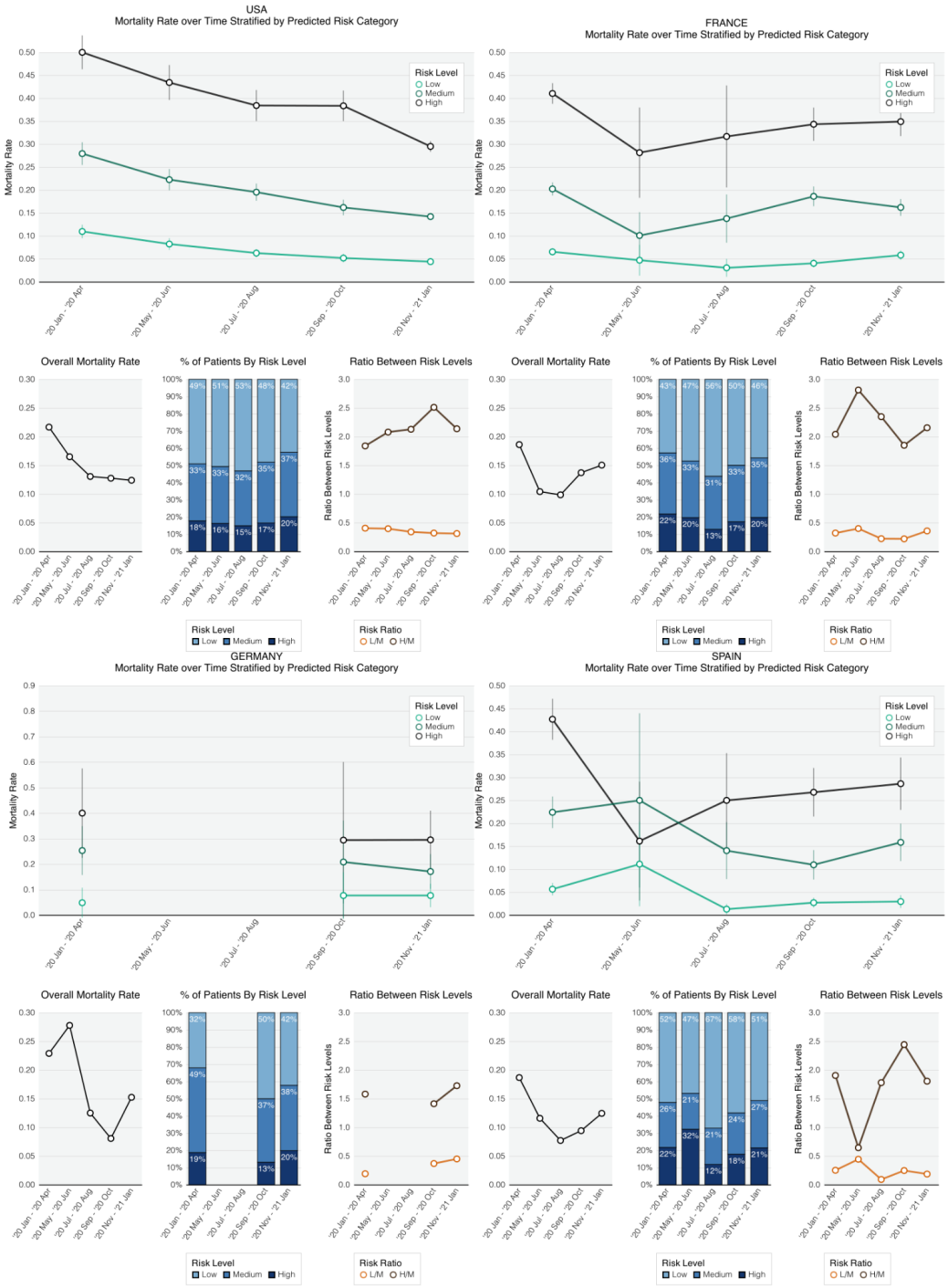
(a) Meta-analysis over all countries.



(b) Country-level AUC over time. AUC was not reported for May–June 2020, and July–August 2020 in Germany due to small counts of death occurring during these months.



eFigure 7. Country-level risk model results w/ event rate information and risk stratification (excluding Italy).



1. Jones AL, Pettey WBP, Carter ME, Brignone E, Redd A, Suo Y, et al. Regional Variations in Documentation of Sexual Trauma Concepts in Electronic Medical Records in the United States Veterans Health Administration. AMIA Annu Symp Proc. 2019;2019: 514–522.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8 8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Secondary Subject Heading:	Public health, Health informatics, Infectious diseases
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Changes in laboratory value improvement and mortality rates over the course of the pandemic: an international retrospective cohort study of hospitalized patients infected with SARS-CoV-2

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Word count: 3930

ABSTRACT:

OBJECTIVE: To assess changes in international mortality rates and laboratory recovery rates during hospitalization for patients hospitalized with SARS-CoV-2 between the first and second waves of the COVID-19 pandemic.

DESIGN, SETTING, AND PARTICIPANTS: This is a retrospective cohort study of 83,178 hospitalized patients admitted before or after polymerase chain reaction-confirmed SARS-CoV-2 infection within the Consortium for Clinical Characterization of COVID-19 by EHR (4CE), an international multi-healthcare system collaborative of 288 hospitals in the United States (US) and Europe.

PRIMARY and SECONDARY OUTCOMES MEASURES: The primary outcome was all-cause mortality rate within 28 days after hospitalization stratified by predicted low, medium, and high mortality risk at baseline. The secondary outcome was the average rate of change in laboratory values during the first week of hospitalization.

RESULTS: Baseline Charlson comorbidity index and laboratory values at admission were not significantly different between the first and second waves. The improvement in laboratory values over time was faster in the second wave compared to the first. The average CRP rate of change was –4.72 vs. –4.14 mg/dL per day (p=0.05). The mortality rates within each risk category significantly decreased over time, with the most substantial decrease in the high-risk group (42.3% in March–April 2020 vs 30.8% in November 2020–January 2021, p<0.001) and a moderate decrease in the intermediate-risk group (21.5% in March–April 2020 vs. 14.3% in November 2020–January 2021, p<0.001).

CONCLUSIONS: Admission profiles of patients hospitalized with SARS-CoV-2 infection did not differ greatly between the first and second waves of the pandemic, but there were notable differences in laboratory improvement rates during hospitalization. Mortality risks among

patients with similar risk profiles decreased over the course of the pandemic. The improvement in laboratory values and mortality risk was consistent across multiple countries.

STRENGTHS AND LIMITATIONS:

- Our federated approach avoided privacy concerns and regulatory barriers common in multicentre studies while facilitating timely international analyses of 83,178 patients from five countries.
- Our common data model along with iterative quality control efforts provide assurance on harmonized data quality.
- The current study may include patients who were either hospitalized due to COVID-19 or had a positive test for SARS-CoV-2 when admitted for an unrelated medical condition.
- For most 4CE participating healthcare systems, we were unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality among inpatients occurs in the hospital and many discharged patients have post-discharge follow-up visits, which allow us to capture 28-day mortality reasonably well.

INTRODUCTION

Mortality rates among hospitalized patients with SARS-CoV-2 infection have decreased over the course of the COVID-19 pandemic [1–5]. It has been hypothesized that this may reflect a higher proportion of younger patients being hospitalized later in the pandemic, but a recently published study reported significant decreases in mortality after stratification by age group [6,7]. A variety of factors are likely responsible, including, but not limited to, improvements in clinical management, resource allocation, and earlier detection of disease [8–15]. There is limited evidence to shed light on these hypotheses; few studies have examined improvements of in-hospital recovery and outcomes over the course of the pandemic. In this international multi-healthcare system retrospective cohort study, we leveraged electronic health records (EHR) data from hospitalized COVID-19 patients[16] to examine temporal shifts in (1) the rate of change for laboratory values towards normal during hospitalization and (2) mortality rates stratified by baseline mortality risk.

METHODS

Individual-level EHR data on hospitalized COVID-19 patients from 18 healthcare systems of the 4CE consortium [17] were extracted and harmonized for this study. Supplementary Table 1 reports further metadata on the participating healthcare systems, which represent 288 hospitals across five countries: France, Germany, Italy, Spain, and the US. Each healthcare system ran the analyses locally and reported summary results to the central institution for federated analyses. Institutional review board approval was obtained at each healthcare system. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [18].

Cohort Identification and Data Collection

Our study included 83,178 patients admitted 7 days before to 14 days after the date of their first positive reverse transcription-polymerase chain reaction SARS-CoV-2 test result recorded in their EHR. We included patients admitted between March 1, 2020 and January 31, 2021 with follow-up data up to June 2021.

We obtained patient-level data on demographics including age groups (18-25, 26-49, 50-69, 70-80, 80+), sex, and race; laboratory test values during hospitalization; International Classification of Disease (ICD) codes, date of discharge, and mortality information. Only US sites reported race. We calculated the Charlson comorbidity index (CCI) based on ICD codes [19–21]. We focused on ten laboratory tests: C-reactive protein (CRP), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, D-dimer, white blood cell count, lymphocyte count, and neutrophil count [10,22–26]. A schematic of our workflow is presented in eFigure 1.

Primary and Secondary Outcomes

We defined all-cause mortality up to 28 days after the admission date as the primary outcome and excluded patients who died on the day of admission in the survival analysis. Each 4CE healthcare system used local criteria to identify in-hospital mortality. We defined laboratory test values during hospitalization as secondary outcomes.

Statistical Analysis

To assess temporal changes over the course of the pandemic, we performed stratified analyses by every two calendar months and between two waves of the pandemic, wherein we defined the first wave as from March 1 to June 30, 2020 and the second wave as from July 1, 2020 to January 31, 2021.

We summarized demographic characteristics, the average CCI at admission, hospitalization duration, and absolute mortality risk over time. Since the VA population has a distinct demographic composition, we reported demographic summaries excluding the VA. We further compared the distributions of admission laboratory values between the two waves.

To summarize the laboratory trajectories during hospitalization, we fit log-linear mixed effects models to the longitudinal laboratory data with cubic splines for time since admission, where we used three knots at days 3, 7, and 17 in the fixed effects to capture nonlinear trends. Since laboratory trajectories may vary by how quickly patients recover, we stratified the trajectory analysis by the hospitalization duration ≤1 week, 1-2 weeks, and 2+ weeks. For each laboratory test, we summarized the *average daily rate of change during the first week of hospitalization* in the first and second waves, denoted by R_1 and R_2. The laboratory trajectory analyses only included data from the US, France, and Spain since few patients from the Germany and Italy sites had repeated laboratory tests.

To study temporal changes in mortality risks, we fit LASSO penalized Cox proportional hazard models for mortality using baseline covariates adjusted for calendar time of the admission date [27,28]. We considered three sets of covariates: (1) age, sex, and race; (2) the ten laboratory tests; and (3) CCI. We modeled the calendar time effect using a cubic spline with knots every 2 weeks. We performed a $\log_e$-transformation to D-dimer, CRP, and ALT due to the skewness in their distributions. Due to the high correlation between ALT and AST, we include AST to ALT ratio (AST/ALT) and $\log_e$ALT as measures of liver function [29,30] instead of $\log_e$AST and $\log_e$ALT. We imputed missing baseline laboratory measures and CCI via the multivariate imputation by chained equation method and averaged over five imputed sets [31]. The mortality

analyses excluded Italy since a very small number of deaths occured after April 2020 in the participating healthcare systems.

Using the trained penalized Cox model, we obtained a mortality risk score for each patient constructed using their baseline covariates. The candidate covariates included in the model training were determined according to existing clinical knowledge. We calculated the area under the receiver operating characteristic curve (AUC) of the risk score for predicting 28-day mortality [32]. We classified patients into three mortality risk groups according to their risk score: high risk if score > c_{high}, medium risk if score $\in (c_{low}, c_{high})$, and low risk if score $\leq c_{low}$. We chose c_{low} and c_{high} to attain a sensitivity of 85% (c_{low}) and a specificity of 85% (c_{high}) for predicting 28-day mortality, which ensures a good separation between the low-risk and high-risk categories. Stratifying by the calendar time window of the admission date, we calculated the AUC of the risk model, the proportions of patients belonging to each risk category, and their corresponding mortality risks. The accuracy parameters were estimated via ten-fold cross-validation to correct for overfitting [33]. We used bootstrap to estimate standard errors [34].

Patient-level analyses were performed within each 4CE healthcare system to obtain site-specific results. We integrate results from all sites using fixed effects meta-analysis. Since the number of hospitalized patients had a different temporal trend across healthcare systems and across countries, we assigned the same weight across different calendar months for each healthcare system to facilitate effective comparisons between waves. All statistical analyses were performed using R software version 4.0.2.

RESULTS

Characteristics of the Study Cohort

The majority of patients were hospitalized March–April 2020 and November 2020 to January 2021 (Figure 1). The most prevalent age group at any time was ages 50–69. In the US—excluding VA patients which are summarized in eFigure 2—the prevalence of patients who were White increased (49.1% in March–April 2020 to 64.1% in November 2020–January 2021, p<0.001), while the prevalence of patients who were Black decreased (30.0% in March–April

2020 to 17.4% in November 2020–January 2021, p<0.001). The average CCI at admission remained relatively constant across time. The absolute 28-day mortality risk decreased from 20.7% in March–April 2020 to 11.9% in July–August 2020 (p<0.001), then increased slightly to 12.4% in November 2020–January 2021 (p<0.001). The temporal shifts in the number of hospitalized patients, demographics, CCI, and mortality rate were generally consistent across countries (eFigure 2).

As shown in Figure 2, observed CRP, creatinine, and D-dimer values at admission were lower in the first wave compared to the second but these differences were not statistically significant. The between-wave CRP mean difference was higher for France (18.5 mg/dL; 95% CI, 16.5-20.5) and Spain (8.4 mg/dL; 95% CI, 4.8-12.0) compared to the US (7.5 mg/dL; 95% CI, 6.1-8.8) and Germany (6.7 mg/dL; 95% CI, –2.5-16.1) (eFigure 3).

Change in Laboratory Trajectory During Hospitalization

Patients' laboratory trajectories during hospitalization improved faster in the second wave compared to the first (Figure 3). CRP values decreased more rapidly (R_1= –4.14 vs. R_2= –4.72 mg/dL per day, p=0.05), while D-dimer values increased substantially faster during the first wave but remained relatively stagnant during the second (R_1=21.01 vs. R_2=1.25 ng/dL per day, p<0.001).

Hospitalization duration decreased, with 53.4% of patients discharged within 1 week in the second wave compared to 49.2% in the first (p<0.001). Patients hospitalized for longer generally had worse laboratory profiles compared to those with shorter stays. The average day-3 CRP among those hospitalized for ≤ 1week and 2+ weeks was 41.68 and 63.64 mg/dL (p<0.001) during the first wave and 27.33 and 43.52 mg/dL (p<0.001) during the second wave. The between-wave difference in the rate of decline, $\Delta_R=R_1-R_2$, also varied by the duration of hospitalization. For CRP, Δ_R was 1.01 (p<0.001), 2.04 (p<0.001) and 0.95 (p=0.001) mg/dL per day among those hospitalized for ≤ 1, 1-2, and 2+ weeks, respectively. For creatinine and D-dimer, Δ_R had similar patterns but were not statistically significant.

Improvement in laboratory values was more pronounced in the US than in France and Spain (eFigure 4). For CRP, Δ_R = 1.07 mg/dL per day (95% CI, 0.86-1.28) in the US, which is significantly higher than that of France (–0.69 mg/dL per day, 95% CI, –1.08- 2.92), and Spain (–0.3 mg/dL per day, 95%CI,–0.79-0.19). The reduction in hospitalization duration varied greatly between countries. The proportion of patients discharged within 1 week increased in the second wave compared to the first in the US (53.4% vs 61.1%, p<0.001), Italy (2.5% vs 14.9%, p<0.001), Germany (32.7% vs 48.6%, p<0.001), and Spain (57.1% vs 62.3%, p<0.001), but decreased in France (46.1% vs 42.4%, p<0.001).

Temporal Changes in Mortality Risk

In our survival analysis, the variables significantly associated with increased risk of mortality were older age, male sex, CCI, lower albumin and lymphocyte count, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT at baseline (Figure 4). The hazard ratios of these risk factors were concordant between countries (eFigure 5).

Over the course of the pandemic, the models' predictive capabilities did not significantly change with AUC ranging from 0.752 to 0.787; the temporal patterns were similar across countries (eFigure 6).

The proportion of high-risk patients decreased from March-April 2020 to July-August 2020 but gradually increased from September 2020 to January 2021 (Figure 5). However, the mortality rates within each risk category decreased over calendar time, with the decrease from March–April 2020 to November 2020–January 2021 most substantial in the high-risk category (47.1% vs. 30.8%, p <0.001), moderate in the intermediate-risk (25.6% vs. 14.8%, p <0.001), and the low-risk (9.5% vs 4.7%, p<0.001) categories. From March–April 2020 to November 2020–January 2021, the US had a more consistent decrease over time while France and Spain decreased from March–April 2020 to July–August 2020 but plateaued afterwards (eFigure 7). In the high-risk category, the decrease in mortality risk from March–April 2020 to July–August 2020 was the highest in Spain (42.7% vs 25.0%, p=0.002), followed by the US (50.0% vs 38.4%, p<0.001), and France (40.1% vs. 31.7%, p=0.11). By November 2020–January 2021, the

mortality risk further decreased to 29.5% (95% CI, 28.3-30.7) in the US, but slightly increased to 34.9% (95% CI, 31.7-38.0) in France and 28.6% (95% CI, 22.9-34.3) in Spain.

DISCUSSION

In this large, international, multi-healthcare system retrospective cohort study, we found decreasing mortality rates and faster physiological recovery based on laboratory profiles between the first and second wave of the COVID-19 pandemic. Given the minimal changes in patient demographic and clinical profiles at admission between the two waves, , our findings cannot be entirely explained by a less severely ill cohort of patients admitted in the second wave [7,35–37]. Given that no new major effective pharmacologic therapies were introduced between the two waves, we could not attribute the difference to new pharmacologic therapies either [38–47]. Potential explanations for the differences between the two waves include timing for emergency visits and hospital admissions, iterative improvement in management strategies of the severe cases, and increased preparedness of healthcare systems in the latter stages of the pandemic. As diverse healthcare systems and populations in different countries learned to improve the care of patients with COVID-19 through diverse experiences, knowledge rapidly disseminated. For example, hospitals may have benefited from improved resource allocation strategies and management in smaller surges in hospitalizations[48]. Negative trial data for hydroxychloroquine, azithromycin, and other pharmacologic agents may have led to reduced usage of these drugs and reduced drug-related adverse effects over the course of the pandemic [40,49–52]. Further investigations into the potential explanations are warranted as this study was not designed to infer the specific reasons for this improvement.

Overall, we observed greater improvements in positive and negative acute phase reactants and markers of organ function (e.g., creatinine, ALT, and AST) in the second wave compared to the first, which suggests that systemic inflammation and multiorgan dysfunction all improved faster in the second wave. Interestingly, we observed greater improvements in CRP, ALT, AST, and creatinine in the second wave in patients with longer hospitalizations; while this may be reflective of a sicker patient population, this could be due to time-dependent (i.e., survivor) bias [53]. Alternatively, there may have been increased corticosteroid use in patients with severe

COVID-19 in the second wave following preliminary results of the RECOVERY trial, which may have improved inflammatory markers and mortality [14,54,55]. In addition, there may have been increased remdesivir in combination with dexamethasone between the first and second waves that may confound these associations [13,54]. Further studies are warranted to investigate the alteration of biochemical trajectories of dexamethasone with remdesivir in contrast to dexamethasone or remdesivir monotherapy [56]. It is also unclear why we observed between-country differences in the between-wave CRP trajectories, whereupon Spain and France had blunted improvement rates; this could certainly be due to differential clinical management across countries.

One potential explanation for the blunted D-dimer trajectories in the second wave compared to the first is increased prophylactic anticoagulation use after the release of International Society on Thrombosis and Haemostasis guidelines in May and September 2020, which recommended prophylactic anticoagulation with low-molecular-weight heparin in all hospitalized patients with COVID-19 who had no anticoagulation contraindications [57]. This may have reduced the higher incidence of thrombotic events observed in the first wave, which could be associated with high D-dimer levels. Furthermore, as D-dimer is often correlated with disease severity and systemic inflammation, increased glucocorticoid use in patients with severe disease could blunt increases in D-dimer [49,58–60].

Our study suggests thatolder age, male sex, higher CCI, low albumin and lymphocyte count values, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT were significantly associated with higher mortality risk. While male sex, older age, and existing comorbidities are established major risk factors for COVID-19-related mortality, our observations of the associations between higher AST/ALT, ALT, and bilirubin with mortality [50,51,61,62] are unique. While derangements in liver function tests are well described in prior studies of patients with COVID-19, the patterns of liver dysfunction associated with worse outcomes have been inconsistent [52,63]. Furthermore, these prior observations tended to be derived from single-center studies which likely introduce significant sources of bias. In particular, our observation of a combination of elevated markers of cholestatic liver function (bilirubin, AST/ALT ratio), inflammatory markers, and cell counts suggests that cholestatic liver

dysfunction may be involved in the disease course, as is observed in patients who are critically ill [64–66]. Furthermore, emerging, though limited, COVID-19 post-mortem studies have suggested that SARS-CoV-2 may directly infect hepatocytes and lead to altered bile duct morphology, reinforcing the possible role of viral-induced cholestatic hepatitis in severe COVID-19 [66]. Alternatively, medication-related liver injury could certainly contribute to liver dysfunction. Future investigations utilizing patient-level data validated by thorough chart review is warranted to better define these associations.

Although cross-country and cross-healthcare-system heterogeneities exist in demographics and laboratory distributions, we observed concordant improvement patterns in both laboratory recovery during hospitalization and mortality risk over time across different countries. However, the admission profile-adjusted temporal change in mortality risk over calendar months differed slightly between the US and Europe (Spain and France). In addition to an increase in hospitalization duration in the latter half of the pandemic in France, in Spain and France the mortality risk plateaued overall and actually increased in the high-risk group. Further investigation into these between-country differences in mortality using chart review and other validation steps is warranted.

Limitations

This study has several limitations. First, similar to other EHR-based studies, the current study might have included patients with incidental hospitalization (i.e., a positive test for SARS-CoV-2 when admitted for an unrelated medical condition) [67]. Further, information regarding each patient's in-hospital care settings, such as admission to intensive care units and their specific respiratory status was not available. Second, most 4CE participating healthcare systems were unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality occurs in the hospital, and most discharged patients would have post-discharge follow-up visits, which would reasonably capture 28-day mortality. A further limitation was the lack of data on patient-specific timing of symptom onset relative to hospital course. Additionally, our study may have potential time-dependent bias given that 4CE defines a first hospital admission that occurs between 7 days before and up to 14 days after the first positive SARS-CoV-2 PCR test. This may also affect the results stratified by duration of hospitalization. Future analyses accounting for

medication administration and procedure use and the subsequent effect on inflammatory markers and creatinine are necessary to infer why these outcomes improved in the second wave.

CONCLUSION

Patients' admission profiles did not differ substantially between waves of the COVID-19 pandemic, but there were notable differences in laboratory recovery rates and mortality in the second wave compared to the first.

ETHICS STATEMENT

All study sites were responsible for and obtained ethics approval, as needed, from the appropriate ethics committee at their institution. IRB protocols were reviewed and approved at APHP (IRB00011591, Project CSE-20-29_ClinicalCOVID), Bordeaux University Hospital (Registration #CHUBX2020RE0253), ICSM (Protocol #2518 CE), Mass General Brigham (IRB#2020P001483), Northwestern University (IRB# STU00212845), University of Kansas (STUDY00146505), University of Freiburg (Application #255/20, Process #210587), and at VA North Atlantic, Southwest, Midwest, Continental, and Pacific (IRB # 3310-x).

The research was determined to be exempt at Hospital Universitario 12 de Octubre (Protocol #20/403), University of Michigan (IRB# HUM00184357), Beth Israel Deaconess Medical Center (IRB# 2020P000565), University of Pittsburgh (STUDY20070095), and University of Pennsylvania (IRB#842813). University of California Los Angeles determined that this study does not need IRB approval because research using limited data sets does not constitute human subjects research.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

AUTHOR CONTRIBUTIONS

GMW, PA, AGS, NPP, RB, SNM, IK, GAB, and TC contributed to design and conceptualization of the study. GMW, NPP, AM, VT, YL, MRH, RB, LC, FJSV, VB, BM, MM, DAH, SM, KBW, SNM, HE, AM, PT, JGK, RWF, GSO, ZX, SV, LPP, DLM, ERS, MJS, SLZ, DZ, ALMT, BWLT, KYN, PS, KC, YLH, MPJ, NGB, and PSB contributed to data collection. CH, HZ, SL, GMW, PA, BWQT, AGS, CLB, YL, ML, FTB, TTL, XW, WY, AN, VB, BM, MM, DAH, MA, PT, JGK, NG, AD, LPP, RK, DZ, JHH, BKBJ, IK, AMS, GAB, and TC contributed to data analysis and interpretation. All authors contributed to drafting and revision of the manuscript and approved the final manuscript. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DATA SHARING STATEMENT

Only de-identified aggregate data was provided by sites for this study. All aggregate data used in this study are available for download at www.covidclinical.net.

COMPETING INTEREST STATEMENT

There are no competing interests to report.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting, or dissemination plans of the research.

FIGURES and TABLES

Figure 1: Demographic shifts. For demographics variables, we set male sex, age 50-69, and White race as reference groups.

Figure 2: Distribution of laboratory values at admission.

Figure 3: Patient-level laboratory recovery rate.

Figure 4. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

Figure 5. Risk model results w/event rate information and risk stratification.

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Figure 1: Demographic shifts. For demographics variables, we set male sex, age 50-69, and White race as reference groups.

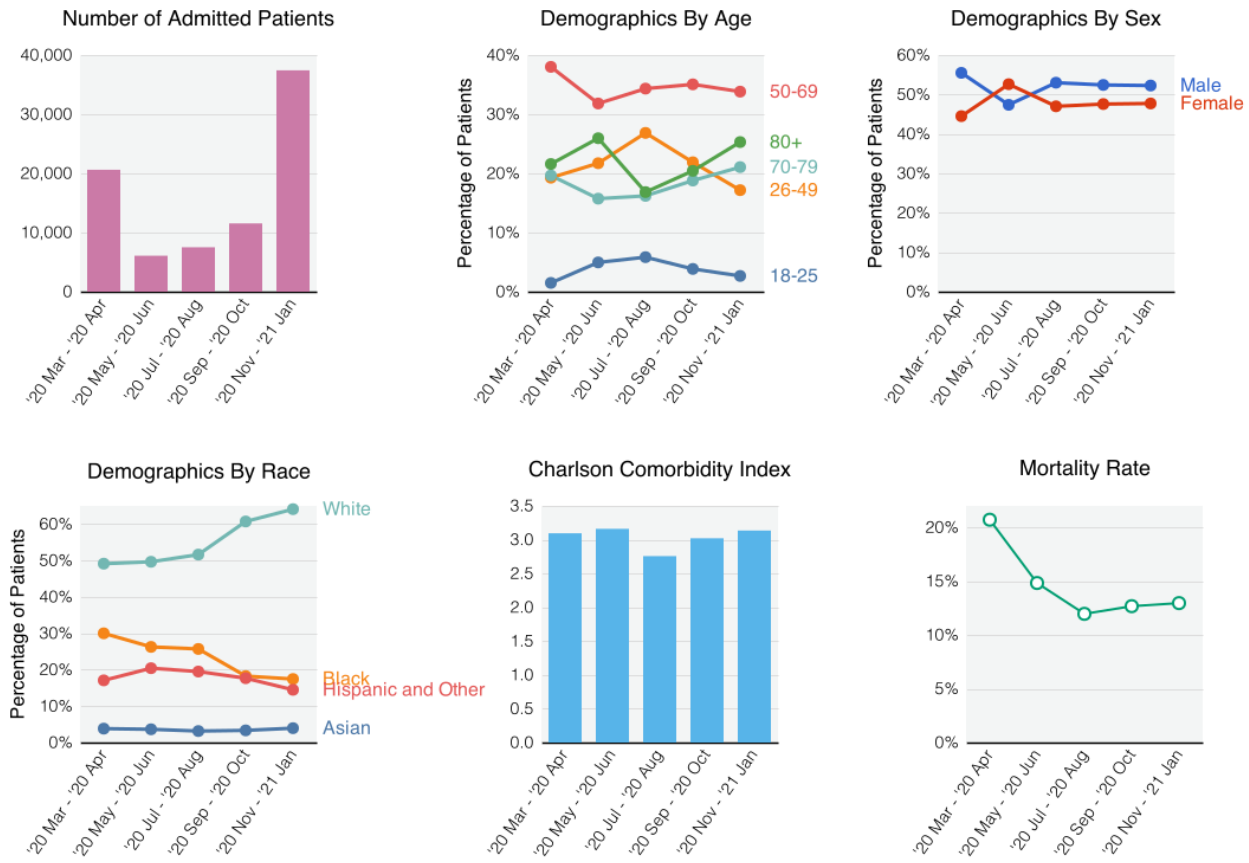


Figure 2: Distribution of laboratory values at admission.

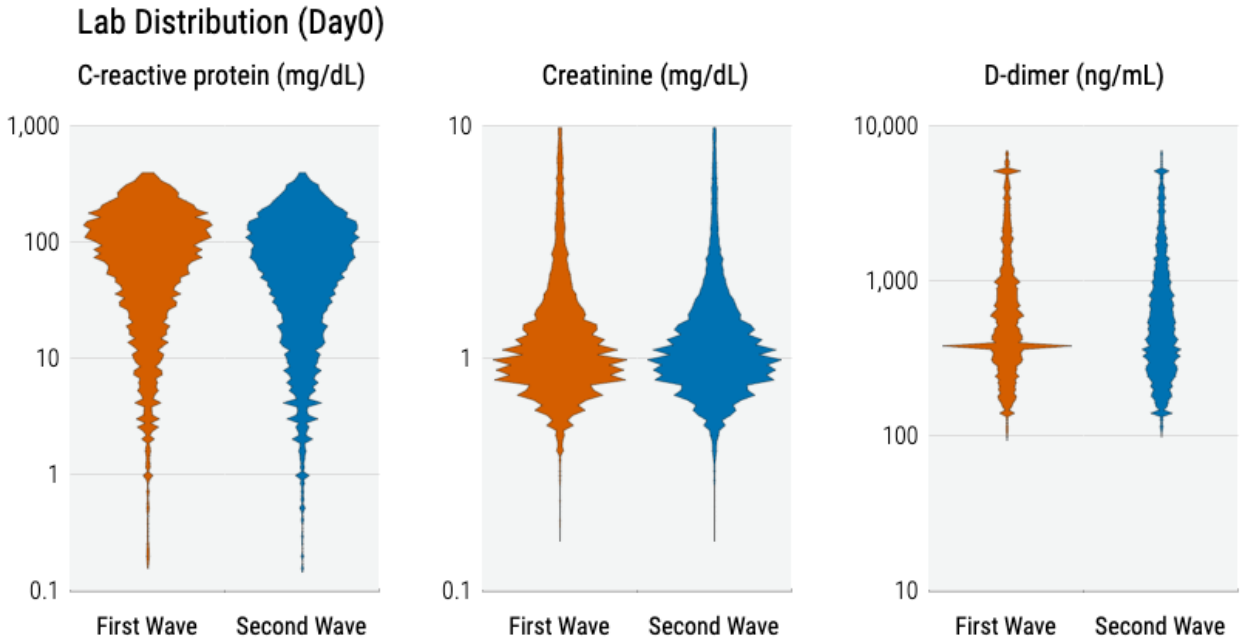


Figure 3: Patient-level laboratory recovery rate.

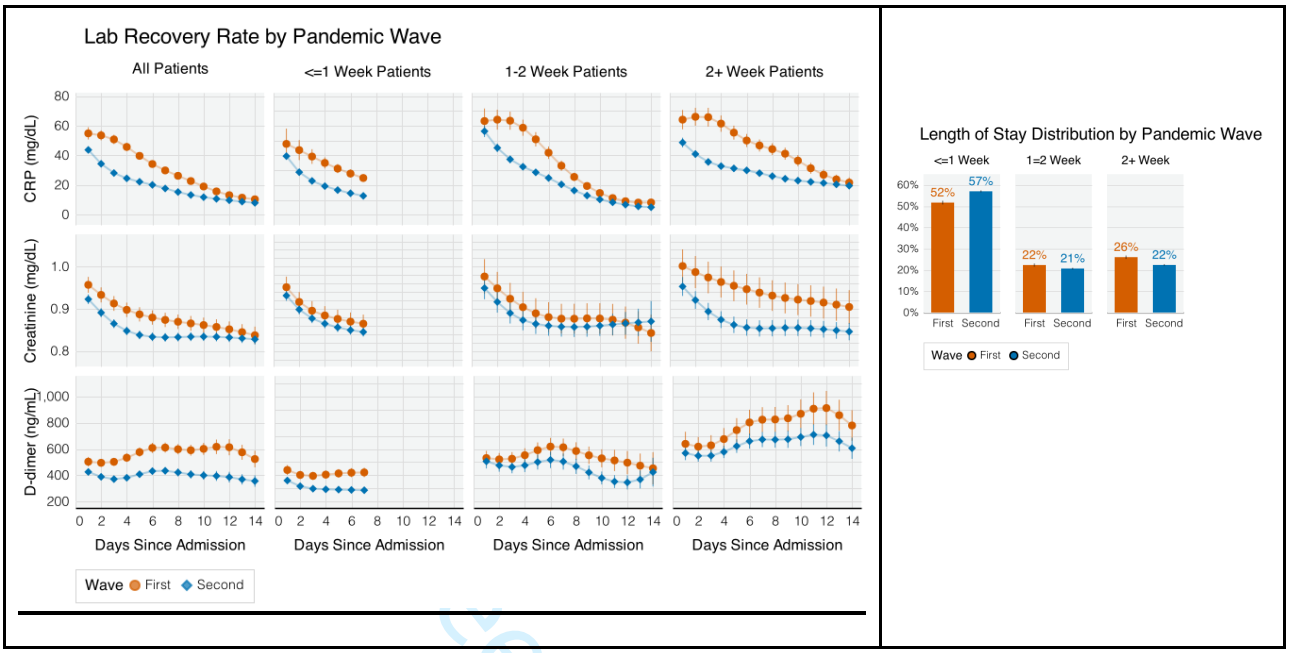


Figure 4. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy)

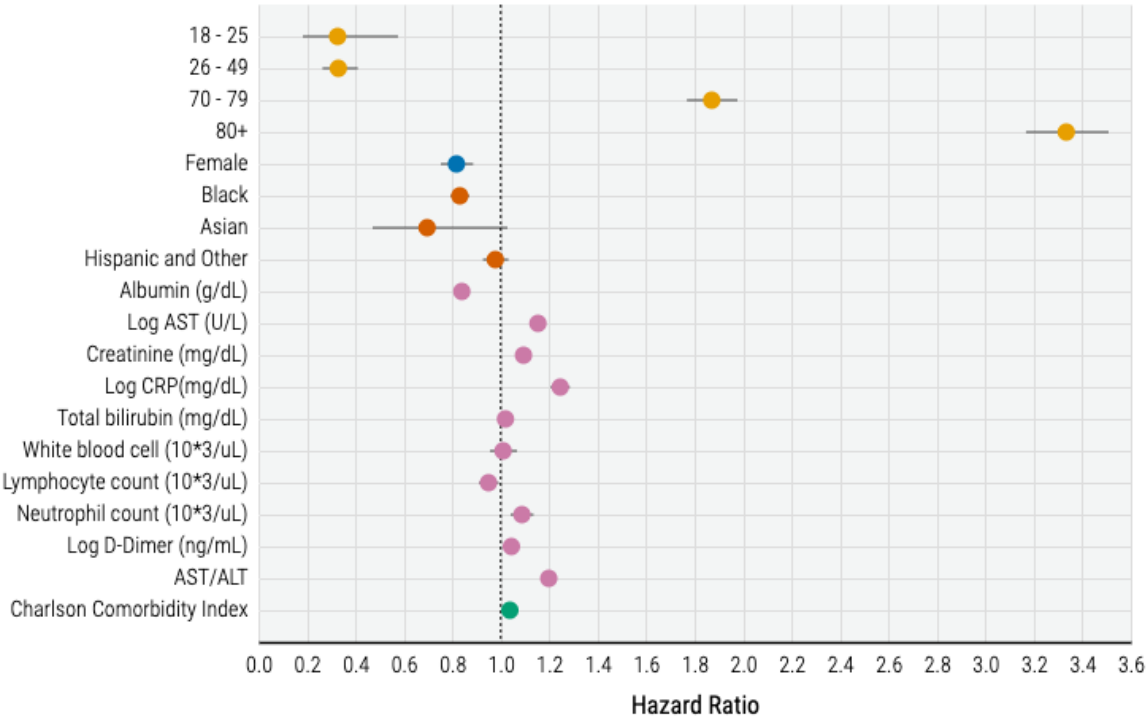
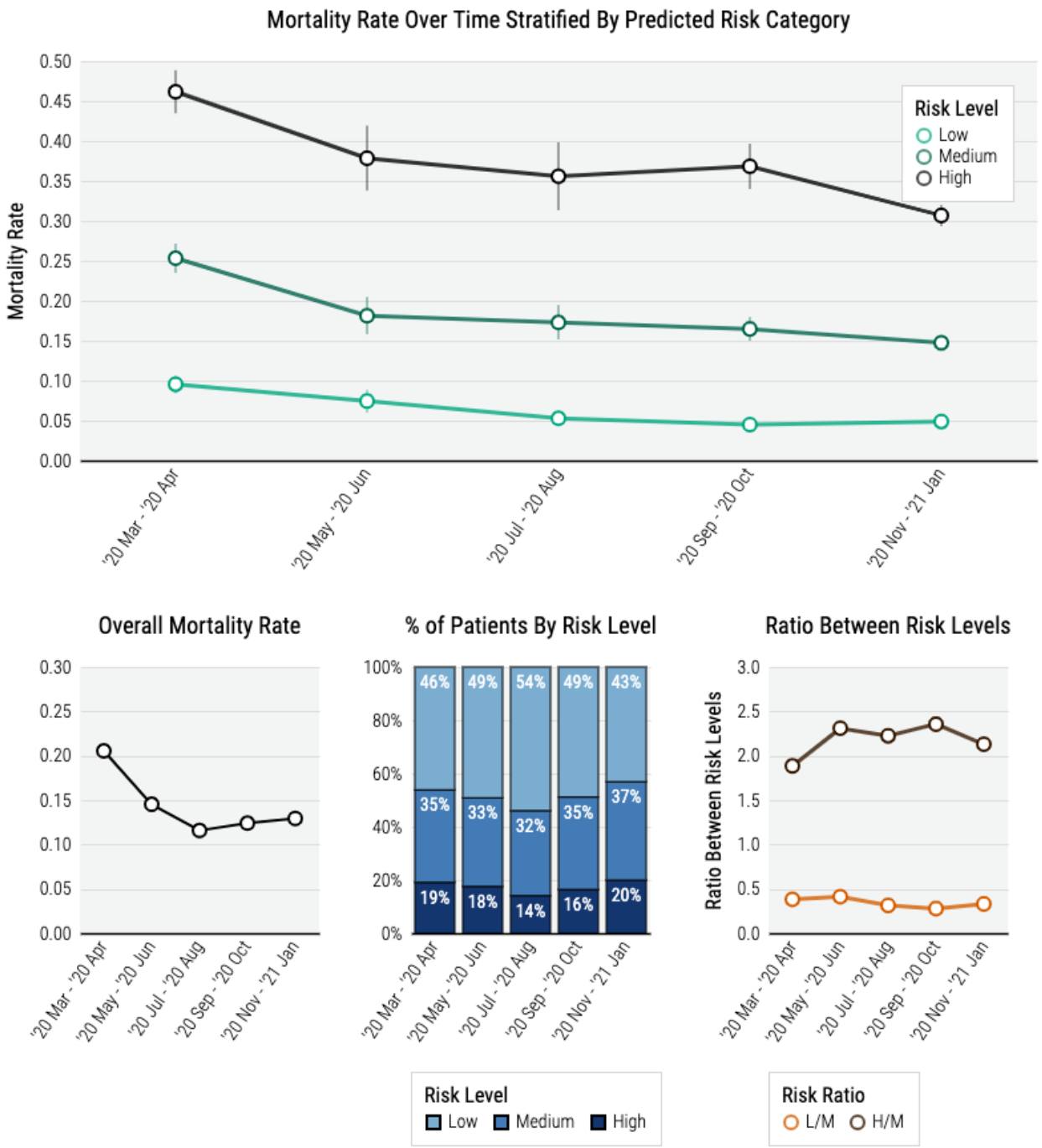


Figure 5: Risk model results w/event rate information and risk stratification.



SUPPLEMENTARY FIGURES

Supplementary eTable 1: Participating hospitals.

Supplementary eFigure 1: Schematic of the federated EHR-based study involving healthcare systems from five countries.

Supplementary eFigure 2: Country-level demographic shifts.

Supplementary eFigure 3: Country-level Distribution of laboratory values at admission.

Supplementary eFigure 4: Patient-level laboratory recovery rate. (a) country-level changes in the recovery rates of laboratory measures (excluding Germany and Italy due to the small number of patients with longitudinal laboratory measurements available); (b) distribution of length of hospital stay among patients admitted in the first wave and in the second wave.

Supplementary eFigure 5: Country-level hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

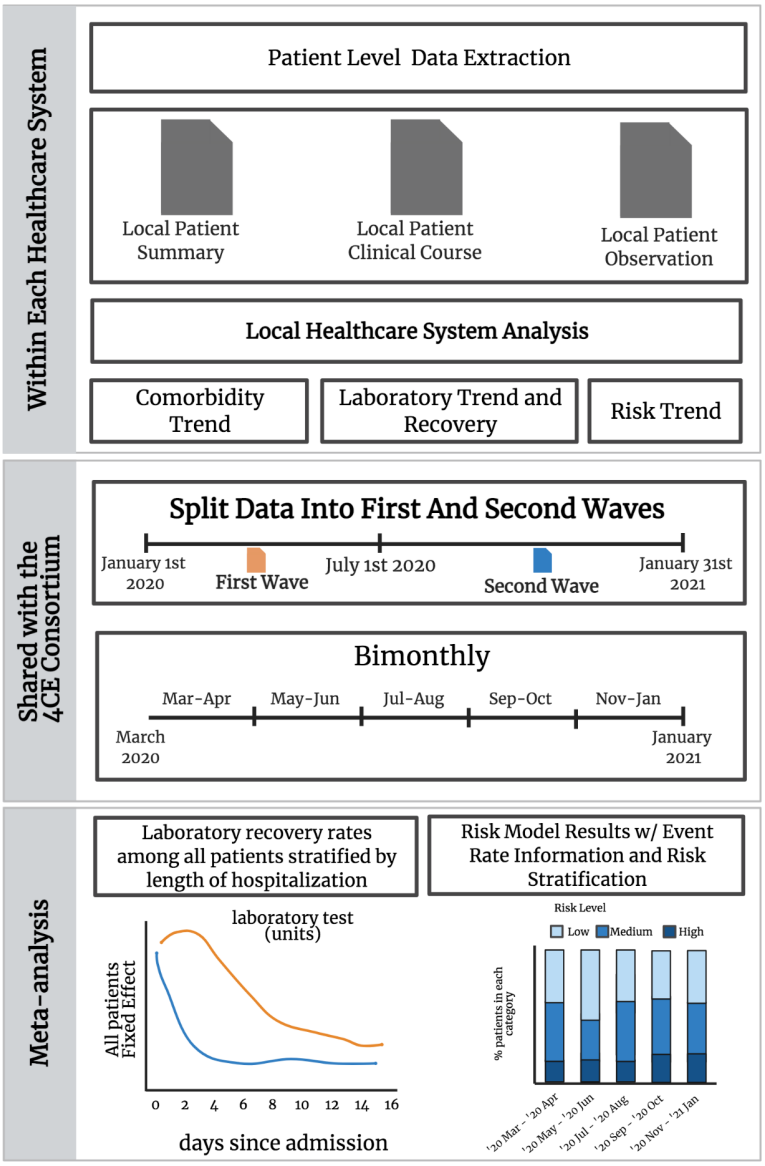
Supplementary eFigure 6. AUC of the Cox regression model for mortality risk prediction (excluding Italy).

Supplementary eFigure 7: Country-level risk model results w/ event rate information and risk stratification (excluding Italy).

eTable 1: Participating healthcare systems.The 170 US Veterans Affairs (VA) hospitals were grouped into 5 regional healthcare systems [1].

Healthcare system	Acronym	Country	City	Hospitals	Beds	Inpatient discharges/ year
Assistance Publique - Hôpitaux de Paris	APHP	France	Paris	39	20 098	1 375 538
Beth Israel Deaconess Medical Center	BIDMC	USA	Boston, MA	1	673	40 752
Bordeaux University Hospital	FRBDX	France	Bordeaux	3	2 676	130 033
Hospital Universitario 12 de Octubre	H12O	Spain	Madrid	1	1 256	45 035
ICSM Hospitals	ICSM	Italy	Pavia/Milan/Lumezzane/Brescia	3	775	12 344
Mass General Brigham (Partners Healthcare)	MGB	USA	Boston, MA	10	3 418	163 521
Northwestern University	NWU	USA	Chicago, IL	10	2 234	103 279
University of California, LA	UCLA	USA	Los Angeles, CA	2	786	40 526
University of Kansas Medical Center	KUMC	USA	Kansas City, KS	1	794	54 659
University of Freiburg, Medical Center	UKFR	Germany	Freiburg	1	1 660	71 500
University of Michigan	UMICH	USA	Ann Arbor, MI	3	1000	49 008
University of Pennsylvania	UPENN	USA	Philadelphia, PA	5	2 469	118 188
University of Pittsburgh	UPITT	USA	Pittsburgh, PA	39	8 085	369 300
VA North Atlantic	VA1	USA		49	3 594	151 075
VA Southwest	VA2	USA		29	3 115	156 315
VA Midwest	VA3	USA		39	2 686	145 468
VA Continental	VA4	USA		24	2 110	113 260
VA Pacific	VA5	USA		29	2 296	114 569
			Total	288	59 725	3 254 370

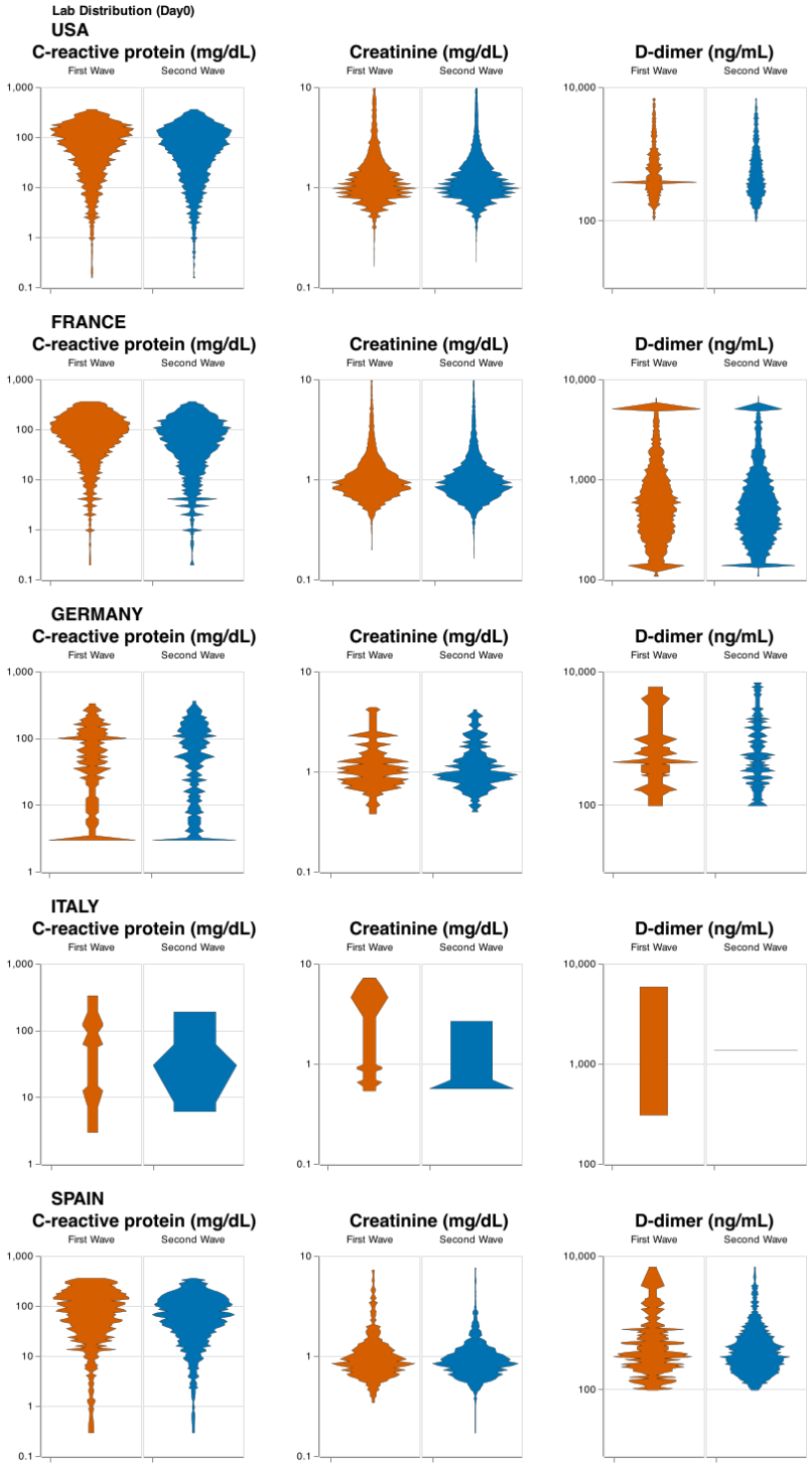
eFigure 1.Schematic of the federated EHR-based study involving healthcare systems from five countries. (created with BioRender.com)



Remark: The hospitalization rate over time tends to differ across regions and across countries, in part due to heterogeneity in a wide range of regional factors including community morbidity and local social distancing policy. This results in different relative sample sizes across healthcare centers over time. To ensure that the temporal trends in clinical presentations summarized via meta-analysis combining all healthcare centers are not driven by the temporal change in the relative sample sizes, we used the same weight for each healthcare center across different calendar months.

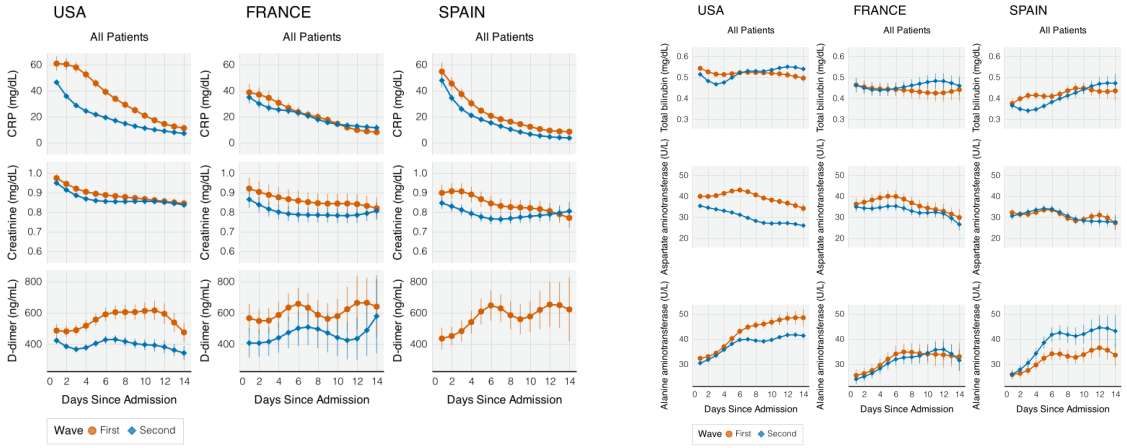
eFigure 2.Country-level demographic shifts.

eFigure 3. Country-level Distribution of laboratory values at admission. The Italy site had a relatively low percentage of patients with laboratory measurements which may have led to less precise estimates in these laboratory changes.

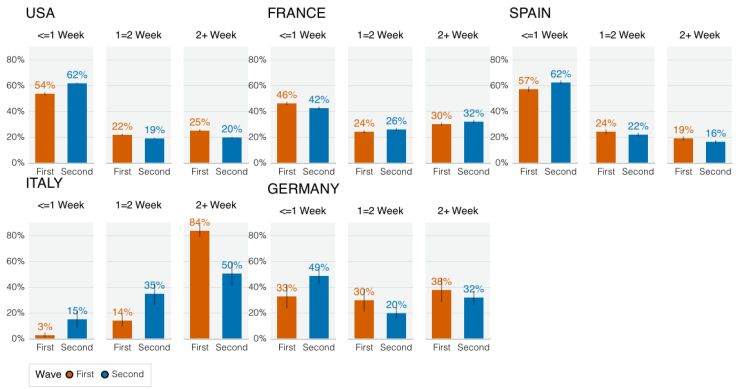


eFigure 4. Patient-level laboratory recovery rate. (a) country-level changes in the recovery rates of laboratory measures (excluding Germany and Italy due to the small number of patients with longitudinal laboratory measurements available); (b) distribution of length of hospital stay among patients admitted in the first wave and in the second wave

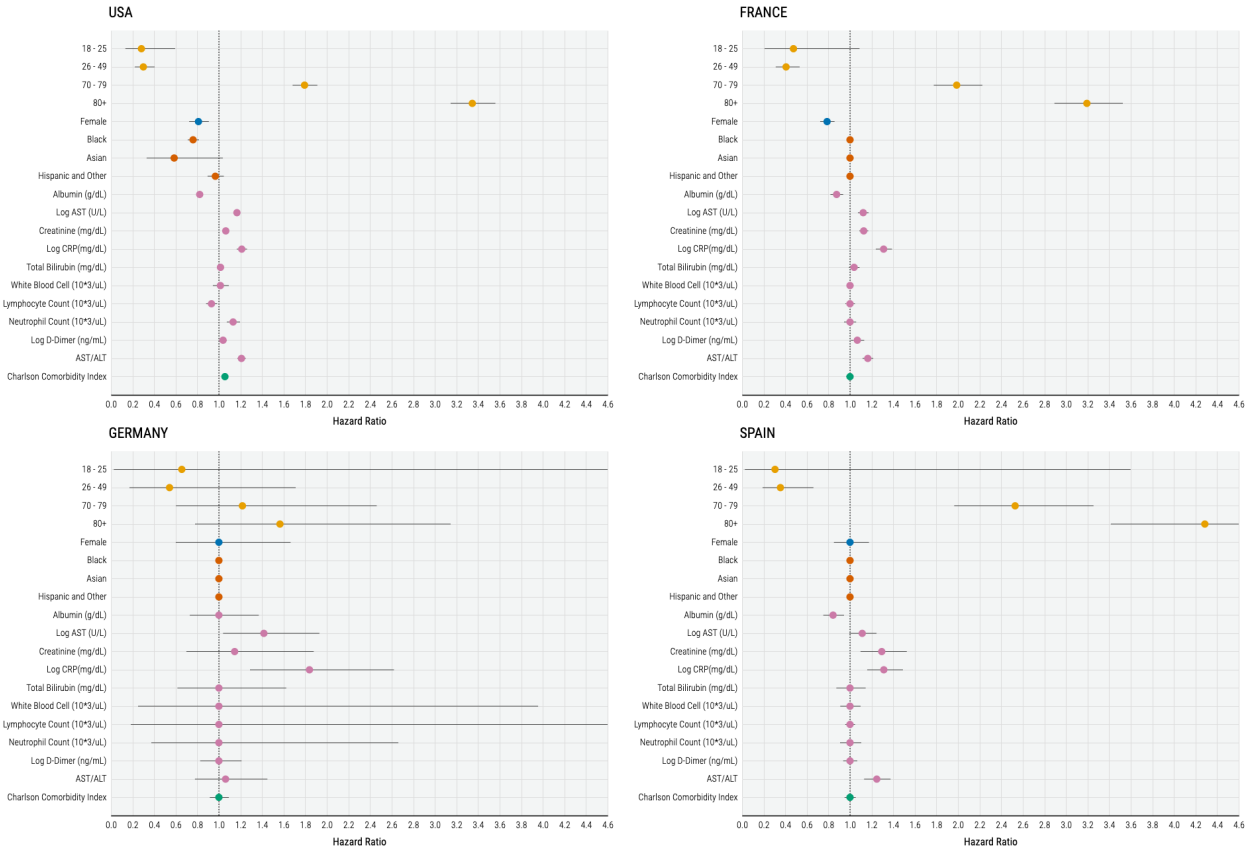
(a) country-level changes in the recovery rates of laboratory measures



(b) Distribution of length of hospital stay among patients admitted in the first wave and in the second wave

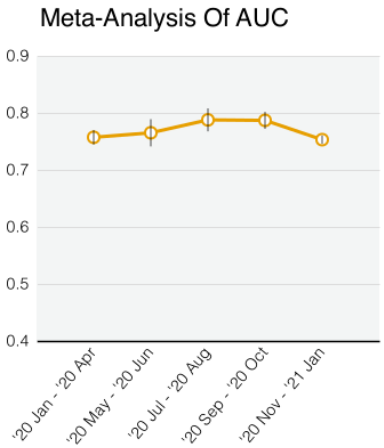


eFigure 5. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

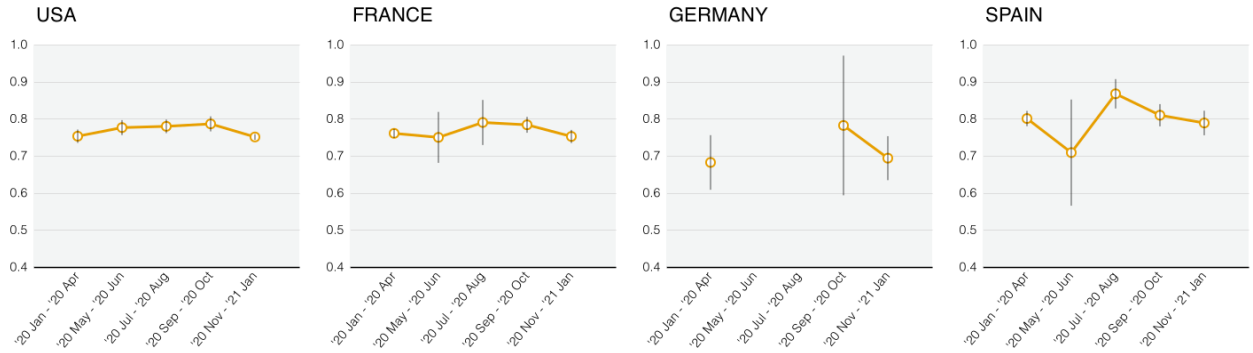

USA
FRANCE
GERMANY
SPAIN
18 - 25
26 - 49
70 - 79
80+
Female
Black
Asian
Hispanic and Other
Albumin (g/dL)
Log AST (U/L)
Creatinine (mg/dL)
Log CRP(mg/dL)
Total Bilirubin (mg/dL)
White Blood Cell (10*3/uL)
Lymphocyte Count (10*3/uL)
Neutrophil Count (10*3/uL)
Log D-Dimer (ng/mL)
AST/ALT
Charlson Comorbidity Index
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6
Hazard Ratio

eFigure 6. AUC of the Cox regression model for mortality risk prediction (excluding Italy).

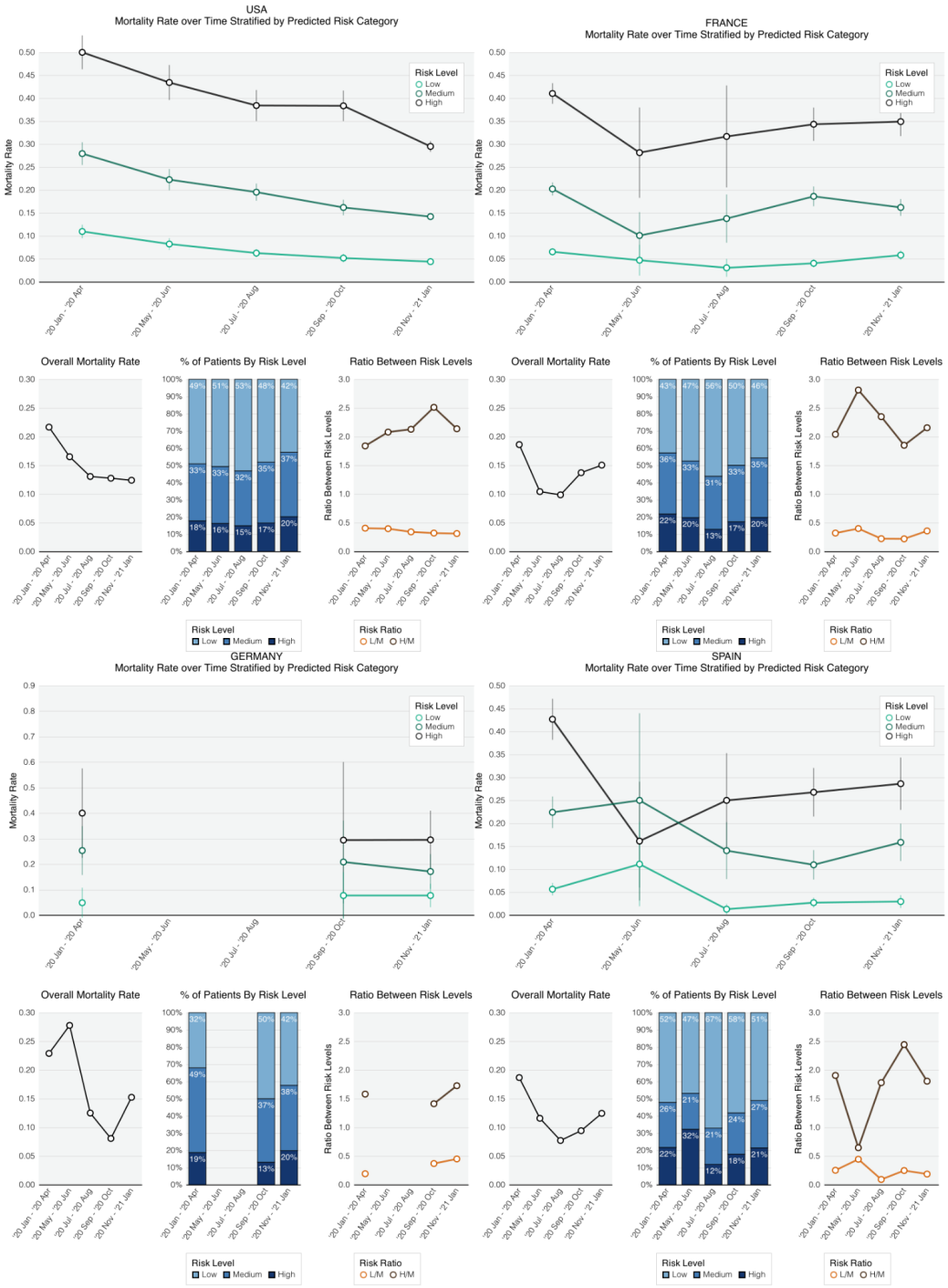
(a) Meta-analysis over all countries.



(b) Country-level AUC over time. AUC was not reported for May–June 2020, and July–August 2020 in Germany due to small counts of death occurring during these months.



eFigure 7. Country-level risk model results w/ event rate information and risk stratification (excluding Italy).



1. Jones AL, Pettey WBP, Carter ME, Brignone E, Redd A, Suo Y, et al. Regional Variations in Documentation of Sexual Trauma Concepts in Electronic Medical Records in the United States Veterans Health Administration. AMIA Annu Symp Proc. 2019;2019: 514–522.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8 8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Changes in laboratory value improvement and mortality rates over the course of the pandemic: an international retrospective cohort study of hospitalized patients infected with SARS-CoV-2

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Secondary Subject Heading:	Public health, Health informatics, Infectious diseases
Keywords:	COVID-19, Public health < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES

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Changes in laboratory value improvement and mortality rates over the course of the pandemic: an international retrospective cohort study of hospitalized patients infected with SARS-CoV-2

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*Hong, Zhang and L'Yi contributed equally

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Word count: 3424

ABSTRACT:

OBJECTIVE: To assess changes in international mortality rates and laboratory recovery rates during hospitalization for patients hospitalized with SARS-CoV-2 between the first wave (March 1 to June 30, 2020) and the second wave (July 1, 2020 to January 31, 2021) of the COVID-19 pandemic.

DESIGN, SETTING, AND PARTICIPANTS: This is a retrospective cohort study of 83,178 hospitalized patients admitted between seven days before or fourteen days after polymerase chain reaction-confirmed SARS-CoV-2 infection within the Consortium for Clinical Characterization of COVID-19 by EHR (4CE), an international multi-healthcare system collaborative of 288 hospitals in the United States (US) and Europe. The laboratory recovery rates and mortality rates over time were compared between the two waves of the pandemic.

PRIMARY and SECONDARY OUTCOMES MEASURES: The primary outcome was all-cause mortality rate within 28 days after hospitalization stratified by predicted low, medium, and high mortality risk at baseline. The secondary outcome was the average rate of change in laboratory values during the first week of hospitalization.

RESULTS: Baseline Charlson comorbidity index and laboratory values at admission were not significantly different between the first and second waves. The improvement in laboratory values over time was faster in the second wave compared to the first. The average CRP rate of change was –4.72 vs. –4.14 mg/dL per day (p=0.05). The mortality rates within each risk category significantly decreased over time, with the most substantial decrease in the high-risk group (42.3% in March–April 2020 vs 30.8% in November 2020–January 2021, p<0.001) and a moderate decrease in the intermediate-risk group (21.5% in March–April 2020 vs. 14.3% in November 2020–January 2021, p<0.001).

CONCLUSIONS: Admission profiles of patients hospitalized with SARS-CoV-2 infection did not differ greatly between the first and second waves of the pandemic, but there were notable differences in laboratory improvement rates during hospitalization. Mortality risks among patients with similar risk profiles decreased over the course of the pandemic. The improvement in laboratory values and mortality risk was consistent across multiple countries.

STRENGTHS AND LIMITATIONS:

- Our federated approach avoided privacy concerns and regulatory barriers common in multicentre studies while facilitating timely international analyses of 83,178 patients from five countries.
- Our common data model along with iterative quality control efforts provide assurance on harmonized data quality.
- The current study may include patients who were either hospitalized due to COVID-19 or had a positive test for SARS-CoV-2 when admitted for an unrelated medical condition.
- For most 4CE participating healthcare systems, we were unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality among inpatients occurs in the hospital and many discharged patients have post-discharge follow-up visits, which allow us to capture 28-day mortality reasonably well.

INTRODUCTION

Mortality rates among hospitalized patients with SARS-CoV-2 infection have decreased over the course of the COVID-19 pandemic [1–5]. It has been hypothesized that this may reflect a higher proportion of younger patients being hospitalized later in the pandemic, but a recently published study reported significant decreases in mortality after stratification by age group [6,7]. A variety of factors are likely responsible, including, but not limited to, improvements in clinical management, resource allocation, and earlier detection of disease [8–15]. There is limited evidence to shed light on these hypotheses; few studies have examined improvements of in-hospital recovery and outcomes over the course of the pandemic. In this international multi-healthcare system retrospective cohort study, we leveraged electronic health records (EHR) data from hospitalized COVID-19 patients[16] to examine temporal shifts in (1) the rate of change for

laboratory values towards normal during hospitalization and (2) mortality rates stratified by baseline mortality risk.

METHODS

Individual-level EHR data on hospitalized COVID-19 patients from 18 healthcare systems of the 4CE consortium [17-18] were extracted and harmonized for this study. Supplementary Table 1 reports further metadata on the participating healthcare systems, which represent 288 hospitals across five countries: France, Germany, Italy, Spain, and the US. Each healthcare system ran the analyses locally and reported summary results to the central institution for federated analyses. Institutional review board approval was obtained at each healthcare system. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [19].

Cohort Identification and Data Collection

Our study included 83,178 patients admitted 7 days before to 14 days after the date of their first positive reverse transcription-polymerase chain reaction SARS-CoV-2 test result recorded in their EHR. We included patients admitted between March 1, 2020 and January 31, 2021 with follow-up data up to June 2021.

We obtained patient-level data on demographics including age groups (18-25, 26-49, 50-69, 70-80, 80+), sex, and race; laboratory test values during hospitalization; International Classification of Disease (ICD) codes, date of discharge, and mortality information. Only US sites reported race. We calculated the Charlson comorbidity index (CCI) based on ICD codes [20–22]. We focused on ten laboratory tests: C-reactive protein (CRP), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, D-dimer, white blood cell count, lymphocyte count, and neutrophil count [10,23–27]. A schematic of our workflow is presented in eFigure 1.

Primary and Secondary Outcomes

We defined all-cause mortality up to 28 days after the admission date as the primary outcome and excluded patients who died on the day of admission in the survival analysis. Each 4CE healthcare system used local criteria to identify in-hospital mortality. We defined laboratory test values during hospitalization as secondary outcomes.

Statistical Analysis

To assess temporal changes over the course of the pandemic, we performed stratified analyses by every two calendar months and between two waves of the pandemic, wherein we defined the first wave as from March 1 to June 30, 2020 and the second wave as from July 1, 2020 to January 31, 2021.

We summarized demographic characteristics, the average CCI at admission, hospitalization duration, and absolute mortality risk over time. Since the VA population has a distinct demographic composition, we reported demographic summaries excluding the VA. We further compared the distributions of admission laboratory values between the two waves.

To summarize the laboratory trajectories during hospitalization, we fit log-linear mixed effects models to the longitudinal laboratory data with cubic splines for time since admission, where we used three knots at days 3, 7, and 17 in the fixed effects to capture nonlinear trends. Since laboratory trajectories may vary by how quickly patients recover, we stratified the trajectory analysis by the hospitalization duration ≤1 week, 1-2 weeks, and 2+ weeks. For each laboratory test, we summarized the *average daily rate of change during the first week of hospitalization* in the first and second waves, denoted by R_1 and R_2. The laboratory trajectory analyses only included data from the US, France, and Spain since few patients from the Germany and Italy sites had repeated laboratory tests.

To study temporal changes in mortality risks, we fit LASSO penalized Cox proportional hazard models for mortality using baseline covariates adjusted for calendar time of the admission date [28-29]. We considered three sets of covariates: (1) age, sex, and race; (2) the ten laboratory tests; and (3) CCI. We modeled the calendar time effect using a cubic spline with knots every 2 weeks. We performed a $\log_e$-transformation to D-dimer, CRP, and ALT due to the skewness in

their distributions. Due to the high correlation between ALT and AST, we include AST to ALT ratio (AST/ALT) and $\log_e$ALT as measures of liver function [30-31] instead of $\log_e$AST and $\log_e$ALT. We imputed missing baseline laboratory measures and CCI via the multivariate imputation by chained equation method and averaged over five imputed sets [32]. The mortality analyses excluded Italy since a very small number of deaths were reported after April 2020 in the participating healthcare systems.

Using the trained penalized Cox model, we obtained a mortality risk score for each patient constructed using their baseline covariates. The candidate covariates included in the model training were determined according to existing clinical knowledge. We calculated the area under the receiver operating characteristic curve (AUC) of the risk score for predicting 28-day mortality [33]. We classified patients into three mortality risk groups according to their risk score: high risk if score > chigh, medium risk if score ∈ (clow, chigh), and low risk if score ≤ clow. We chose clow and chigh to attain a sensitivity of 85% (clow) and a specificity of 85% (chigh) for predicting 28-day mortality, which ensures a good separation between the low-risk and high-risk categories. Stratifying by the calendar time window of the admission date, we calculated the AUC of the risk model, the proportions of patients belonging to each risk category, and their corresponding mortality risks. The accuracy parameters were estimated via ten-fold cross-validation to correct for overfitting [34]. We used bootstrap to estimate standard errors [35].

Patient-level analyses were performed within each 4CE healthcare system to obtain site-specific results. We integrate results from all sites using fixed effects meta-analysis. Since the number of hospitalized patients had a different temporal trend across healthcare systems and across countries, we assigned the same weight across different calendar months for each healthcare system to facilitate effective comparisons between waves. All statistical analyses were performed using R software version 4.0.2.

RESULTS

Characteristics of the Study Cohort

The majority of patients were hospitalized March–April 2020 and November 2020 to January 2021 (Figure 1). The most prevalent age group at any time was ages 50–69. In the US—excluding VA patients which are summarized in eFigure 2—the prevalence of patients who were White increased (49.1% in March–April 2020 to 64.1% in November 2020–January 2021, p<0.001), while the prevalence of patients who were Black decreased (30.0% in March–April 2020 to 17.4% in November 2020–January 2021, p<0.001). The average CCI at admission remained relatively constant across time. The absolute 28-day mortality risk decreased from 20.7% in March–April 2020 to 11.9% in July–August 2020 (p<0.001), then increased slightly to 12.4% in November 2020–January 2021 (p<0.001). The temporal shifts in the number of hospitalized patients, demographics, CCI, and mortality rate were generally consistent across countries (eFigure 2).

As shown in Figure 2, observed CRP, creatinine, and D-dimer values at admission were lower in the first wave compared to the second but these differences were not statistically significant. The between-wave CRP mean difference was higher for France (18.5 mg/dL; 95% CI, 16.5-20.5) and Spain (8.4 mg/dL; 95% CI, 4.8-12.0) compared to the US (7.5 mg/dL; 95% CI, 6.1-8.8) and Germany (6.7 mg/dL; 95% CI, –2.5-16.1) (eFigure 3).

Change in Laboratory Trajectory During Hospitalization

Patients' laboratory trajectories during hospitalization improved faster in the second wave compared to the first (Figure 3). CRP values decreased more rapidly (R_1= –4.14 vs. R_2= –4.72 mg/dL per day, p=0.05), while D-dimer values increased substantially faster during the first wave but remained relatively stagnant during the second (R_1=21.01 vs. R_2=1.25 ng/dL per day, p<0.001).

Hospitalization duration decreased, with 53.4% of patients discharged within 1 week in the second wave compared to 49.2% in the first (p<0.001). Patients hospitalized for longer generally had worse laboratory profiles compared to those with shorter stays. The average day-3 CRP among those hospitalized for ≤ 1week and 2+ weeks was 41.68 and 63.64 mg/dL (p<0.001) during the first wave and 27.33 and 43.52 mg/dL (p<0.001) during the second wave. The between-wave difference in the rate of decline, $\Delta_R=R_1-R_2$, also varied by the duration of

hospitalization. For CRP, Δ_R was 1.01 (p<0.001), 2.04 (p<0.001) and 0.95 (p=0.001) mg/dL per day among those hospitalized for ≤ 1, 1-2, and 2+ weeks, respectively. For creatinine and D-dimer, Δ_R had similar patterns but were not statistically significant.

Improvement in laboratory values was more pronounced in the US than in France and Spain (eFigure 4). For CRP, Δ_R = 1.07 mg/dL per day (95% CI, 0.86-1.28) in the US, which is significantly higher than that of France (–0.69 mg/dL per day, 95% CI, –1.08- 2.92), and Spain (–0.3 mg/dL per day, 95%CI,–0.79-0.19). The reduction in hospitalization duration varied greatly between countries. The proportion of patients discharged within 1 week increased in the second wave compared to the first in the US (53.4% vs 61.1%, p<0.001), Italy (2.5% vs 14.9%, p<0.001), Germany (32.7% vs 48.6%, p<0.001), and Spain (57.1% vs 62.3%, p<0.001), but decreased in France (46.1% vs 42.4%, p<0.001).

Temporal Changes in Mortality Risk

In our survival analysis, the variables significantly associated with increased risk of mortality were older age, male sex, CCI, lower albumin and lymphocyte count, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT at baseline (Figure 4). The hazard ratios of these risk factors were concordant between countries (eFigure 5).

Over the course of the pandemic, the models' predictive capabilities did not significantly change with AUC ranging from 0.752 to 0.787; the temporal patterns were similar across countries (eFigure 6).

The proportion of high-risk patients decreased from March-April 2020 to July-August 2020 but gradually increased from September 2020 to January 2021 (Figure 5). However, the mortality rates within each risk category decreased over calendar time, with the decrease from March–April 2020 to November 2020–January 2021 most substantial in the high-risk category (47.1% vs. 30.8%, p <0.001), moderate in the intermediate-risk (25.6% vs. 14.8%, p <0.001), and the low-risk (9.5% vs 4.7%, p<0.001) categories. From March–April 2020 to November 2020–January 2021, the US had a more consistent decrease over time while France and Spain

decreased from March–April 2020 to July–August 2020 but plateaued afterwards (eFigure 7). In the high-risk category, the decrease in mortality risk from March–April 2020 to July–August 2020 was the highest in Spain (42.7% vs 25.0%, p=0.002), followed by the US (50.0% vs 38.4%, p<0.001), and France (40.1% vs. 31.7%, p=0.11). By November 2020–January 2021, the mortality risk further decreased to 29.5% (95% CI, 28.3-30.7) in the US, but slightly increased to 34.9% (95% CI, 31.7-38.0) in France and 28.6% (95% CI, 22.9-34.3) in Spain.

DISCUSSION

In this large, international, multi-healthcare system retrospective cohort study, we found decreasing mortality rates and faster physiological recovery based on laboratory profiles between the first and second wave of the COVID-19 pandemic. Given the minimal changes in patient demographic and clinical profiles at admission between the two waves, our findings cannot be entirely explained by a less severely ill cohort of patients admitted in the second wave [7,36–38]. There were no new major effective pharmacologic therapies introduced between the two waves[39–48]. However, some existing therapies, such as corticosterids, achieved widespread use as health care providers gained experience with managing the disease. Moreover, evolving protocols for hospital care, including adapted ventilatory support and the higher proportion of patients managed without mechanical ventilation, probably contributed to improving streamlined care and resource allocation. Potential explanations for the differences between the two waves include timing for emergency visits and hospital admissions, iterative improvement in management strategies of the severe cases, and increased preparedness of healthcare systems in the latter stages of the pandemic. As diverse healthcare systems and populations in different countries learned to improve the care of patients with COVID-19 through diverse experiences, knowledge rapidly disseminated. For example, hospitals may have benefited from improved resource allocation strategies and management in smaller surges in hospitalizations[49]. Negative trial data for hydroxychloroquine, azithromycin, and other pharmacologic agents may have led to reduced usage of these drugs and reduced drug-related adverse effects over the course of the pandemic [41,50–53]. Further investigations into the potential explanations are warranted as this study was not designed to infer the specific reasons for this improvement.

Overall, we observed greater improvements in positive and negative acute phase reactants and markers of organ function (e.g., creatinine, ALT, and AST) in the second wave compared to the first, which suggests that systemic inflammation and multiorgan dysfunction all improved faster in the second wave. Interestingly, we observed greater improvements in CRP, ALT, AST, and creatinine in the second wave in patients with longer hospitalizations; while this may be reflective of a sicker patient population, this could be due to time-dependent (i.e., survivor) bias [54]. Alternatively, there may have been increased corticosteroid use in patients with severe COVID-19 in the second wave following preliminary results of the RECOVERY trial, which may have improved inflammatory markers and mortality [14,55,56]. In addition, there may have been increased remdesivir in combination with dexamethasone between the first and second waves that may confound these associations [13,55]. Further studies are warranted to investigate the alteration of biochemical trajectories of dexamethasone with remdesivir in contrast to dexamethasone or remdesivir monotherapy [57]. It is also unclear why we observed between-country differences in the between-wave CRP trajectories, whereupon Spain and France had blunted improvement rates; this could certainly be due to differential clinical management across countries.

One potential explanation for the blunted D-dimer trajectories in the second wave compared to the first is increased prophylactic anticoagulation use after the release of International Society on Thrombosis and Haemostasis guidelines in May and September 2020, which recommended prophylactic anticoagulation with low-molecular-weight heparin in all hospitalized patients with COVID-19 who had no anticoagulation contraindications [58]. This may have reduced the higher incidence of thrombotic events observed in the first wave, which could be associated with high D-dimer levels. Furthermore, as D-dimer is often correlated with disease severity and systemic inflammation, increased glucocorticoid use in patients with severe disease could blunt increases in D-dimer [50,59–61].

Our study suggests thatolder age, male sex, higher CCI, low albumin and lymphocyte count values, and higher CRP, total bilirubin, white blood cell count, neutrophil count, D-dimer, ALT, and AST/ALT were significantly associated with higher mortality risk. While male sex, older age, and existing comorbidities are established major risk factors for COVID-19-related

mortality, our observations of the associations between higher AST/ALT, ALT, and bilirubin with mortality [51,52,62,63] are unique. While derangements in liver function tests are well described in prior studies of patients with COVID-19, the patterns of liver dysfunction associated with worse outcomes have been inconsistent [53,64]. Furthermore, these prior observations tended to be derived from single-center studies which likely introduce significant sources of bias. In particular, our observation of a combination of elevated markers of cholestatic liver function (bilirubin, AST/ALT ratio), inflammatory markers, and cell counts suggests that cholestatic liver dysfunction may be involved in the disease course, as is observed in patients who are critically ill [65–67]. Furthermore, emerging, though limited, COVID-19 post-mortem studies have suggested that SARS-CoV-2 may directly infect hepatocytes and lead to altered bile duct morphology, reinforcing the possible role of viral-induced cholestatic hepatitis in severe COVID-19 [67]. Alternatively, medication-related liver injury could certainly contribute to liver dysfunction. Future investigations utilizing patient-level data validated by thorough chart review is warranted to better define these associations.

Although cross-country and cross-healthcare-system heterogeneities exist in demographics and laboratory distributions, we observed concordant improvement patterns in both laboratory recovery during hospitalization and mortality risk over time across different countries. However, the admission profile-adjusted temporal change in mortality risk over calendar months differed slightly between the US and Europe (Spain and France). In addition to an increase in hospitalization duration in the latter half of the pandemic in France, in Spain and France the mortality risk plateaued overall and actually increased in the high-risk group. Further investigation into these between-country differences in mortality using chart review and other validation steps is warranted.

Limitations

This study has several limitations. First, similar to other EHR-based studies, the current study might have included patients with incidental hospitalization (i.e., a positive test for SARS-CoV-2 when admitted for an unrelated medical condition) [68]. Further, information regarding each patient's in-hospital care settings, such as admission to intensive care units and their specific respiratory status was not available. Second, most 4CE participating healthcare systems were

unable to capture all out-of-hospital mortality. However, most COVID-19-related mortality occurs in the hospital, and most discharged patients would have post-discharge follow-up visits, which would reasonably capture 28-day mortality. A further limitation was the lack of data on patient-specific timing of symptom onset relative to hospital course. Additionally, our study may have potential time-dependent bias given that 4CE defines a first hospital admission that occurs between 7 days before and up to 14 days after the first positive SARS-CoV-2 PCR test. This may also affect the results stratified by duration of hospitalization. Future analyses accounting for medication administration and procedure use and the subsequent effect on inflammatory markers and creatinine are necessary to infer why these outcomes improved in the second wave.

CONCLUSION

Patients' admission profiles did not differ substantially between waves of the COVID-19 pandemic, but there were notable differences in laboratory recovery rates and mortality in the second wave compared to the first.

ETHICS STATEMENT

All study sites were responsible for and obtained ethics approval, as needed, from the appropriate ethics committee at their institution. IRB protocols were reviewed and approved at APHP (IRB00011591, Project CSE-20-29_ClinicalCOVID), Bordeaux University Hospital (Registration #CHUBX2020RE0253), ICSM (Protocol #2518 CE), Mass General Brigham (IRB#2020P001483), Northwestern University (IRB# STU00212845), University of Kansas (STUDY00146505), University of Freiburg (Application #255/20, Process #210587), and at VA North Atlantic, Southwest, Midwest, Continental, and Pacific (IRB # 3310-x).

The research was determined to be exempt at Hospital Universitario 12 de Octubre (Protocol #20/403), University of Michigan (IRB# HUM00184357), Beth Israel Deaconess Medical Center (IRB# 2020P000565), University of Pittsburgh (STUDY20070095), and University of Pennsylvania (IRB#842813). University of California Los Angeles determined that this study

does not need IRB approval because research using limited data sets does not constitute human subjects research.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

AUTHOR CONTRIBUTIONS

GMW, PA, AGS, NPP, RB, SNM, IK, GAB, and TC contributed to design and conceptualization of the study. GMW, NPP, AM, VT, YL, MRH, RB, LC, FJSV, VB, BM, MM, DAH, SM, KBW, SNM, HE, AM, PT, JGK, RWF, GSO, ZX, SV, LPP, DLM, ERS, MJS, SLZ, DZ, ALMT, BWLT, KYN, PS, KC, YLH, MPJ, NGB, and PSB contributed to data collection. CH, HZ, SL, GMW, PA, BWQT, AGS, CLB, YL, ML, FTB, TTL, XW, WY, AN, VB, BM, MM, DAH, MA, PT, JGK, NG, AD, LPP, RK, DZ, JHH, BKBJ, IK, AMS, GAB, and TC contributed to data analysis and interpretation. All authors contributed to drafting and revision of the manuscript and approved the final manuscript. All authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTEREST STATEMENT

There are no competing interests to report.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, or reporting, or dissemination plans of the research.

FIGURES and TABLES

Figure 1: Demographic shifts. For demographics variables, we set male sex, age 50-69, and White race as reference groups.

Figure 2: Distribution of laboratory values at admission.

Figure 3: Patient-level laboratory recovery rate.

Figure 4. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

Figure 5. Risk model results w/event rate information and risk stratification.

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Figure 1: Demographic shifts. For demographics variables, we set male sex, age 50-69, and White race as reference groups.

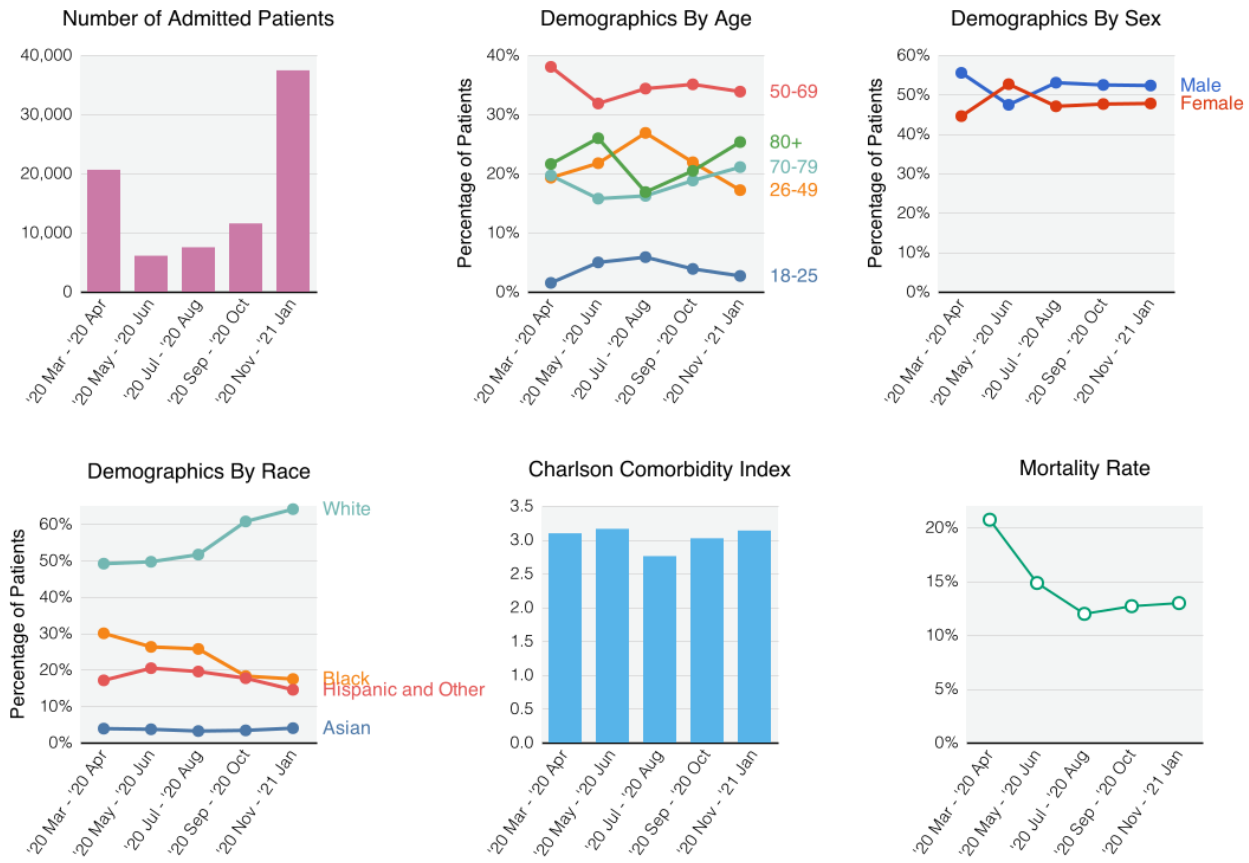


Figure 2: Distribution of laboratory values at admission.

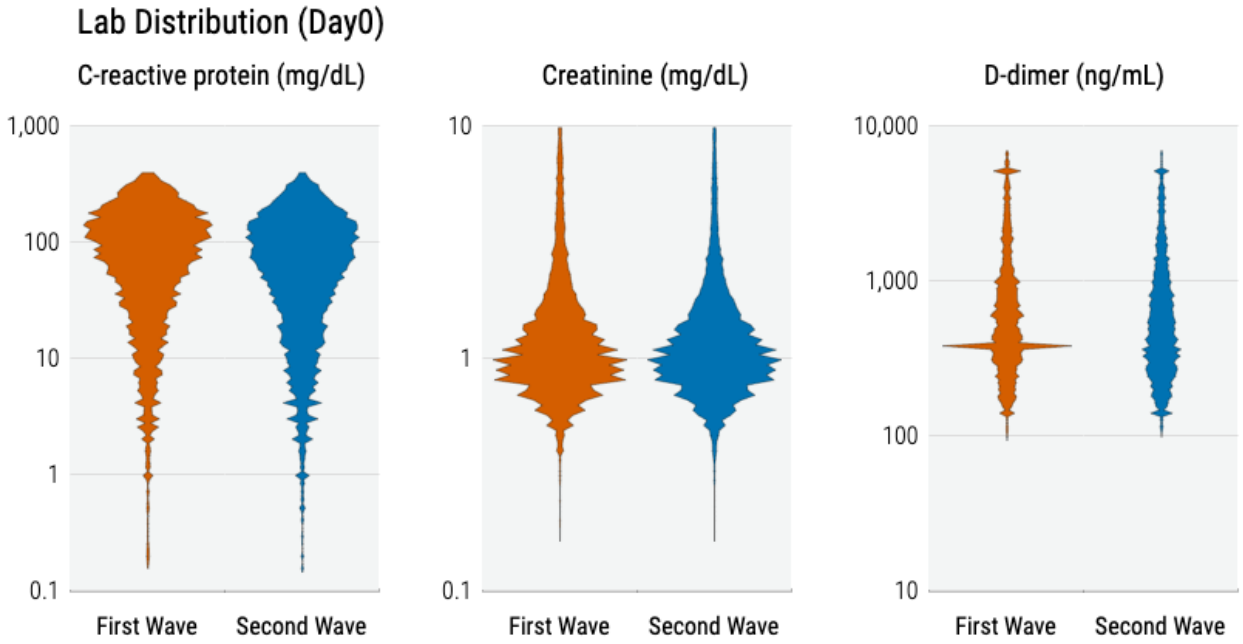


Figure 3: Patient-level laboratory recovery rate.

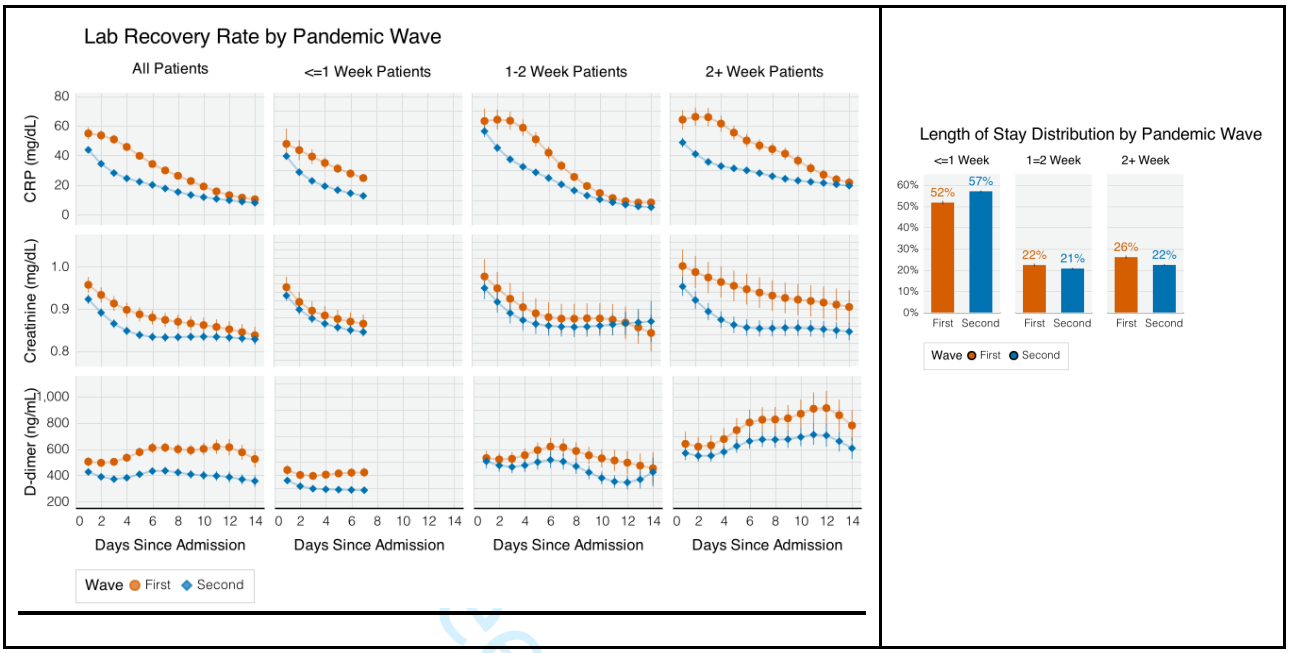


Figure 4. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy)

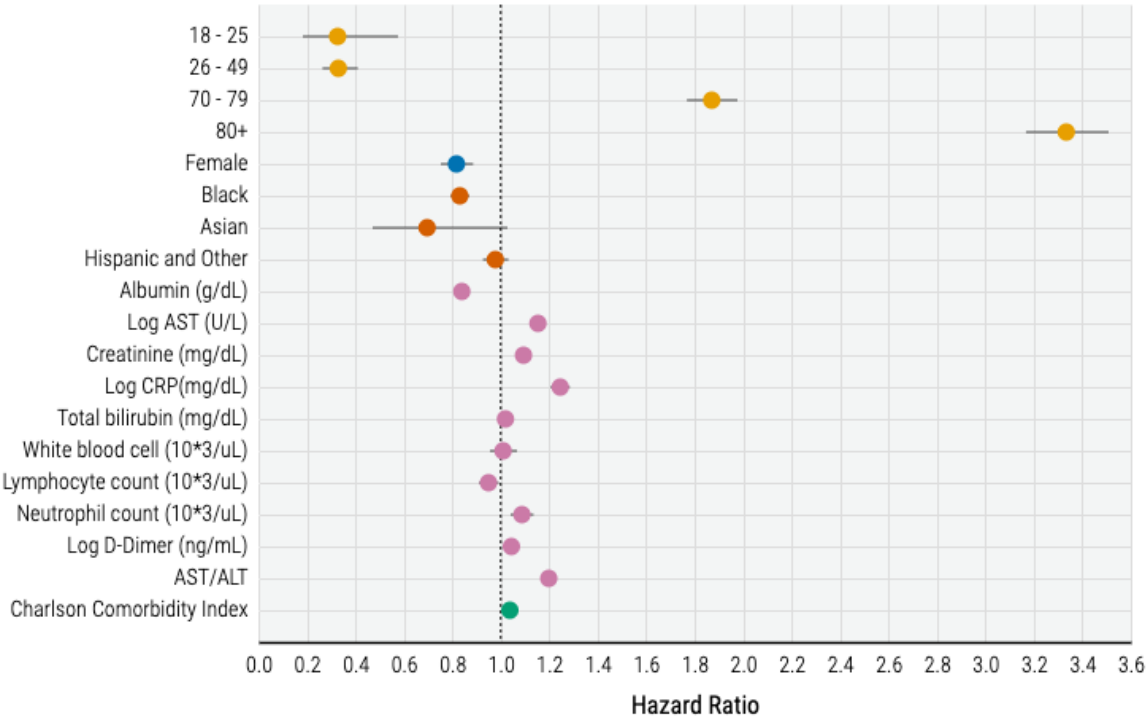
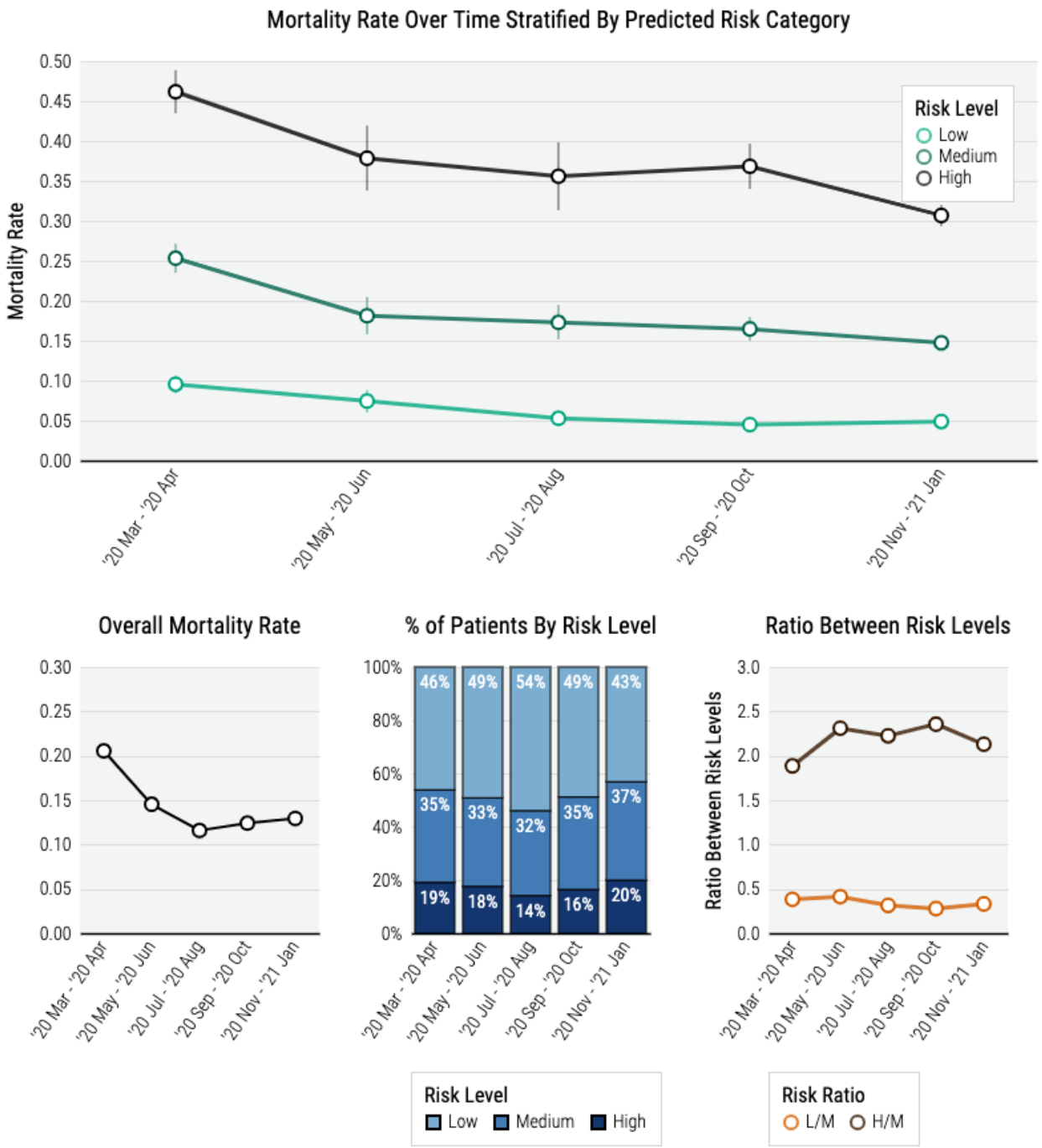


Figure 5: Risk model results w/event rate information and risk stratification.



SUPPLEMENTARY FIGURES

Supplementary eTable 1: Participating hospitals.

Supplementary eFigure 1: Schematic of the federated EHR-based study involving healthcare systems from five countries.

Supplementary eFigure 2: Country-level demographic shifts.

Supplementary eFigure 3: Country-level Distribution of laboratory values at admission.

Supplementary eFigure 4: Patient-level laboratory recovery rate. (a) country-level changes in the recovery rates of laboratory measures (excluding Germany and Italy due to the small number of patients with longitudinal laboratory measurements available); (b) distribution of length of hospital stay among patients admitted in the first wave and in the second wave.

Supplementary eFigure 5: Country-level hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

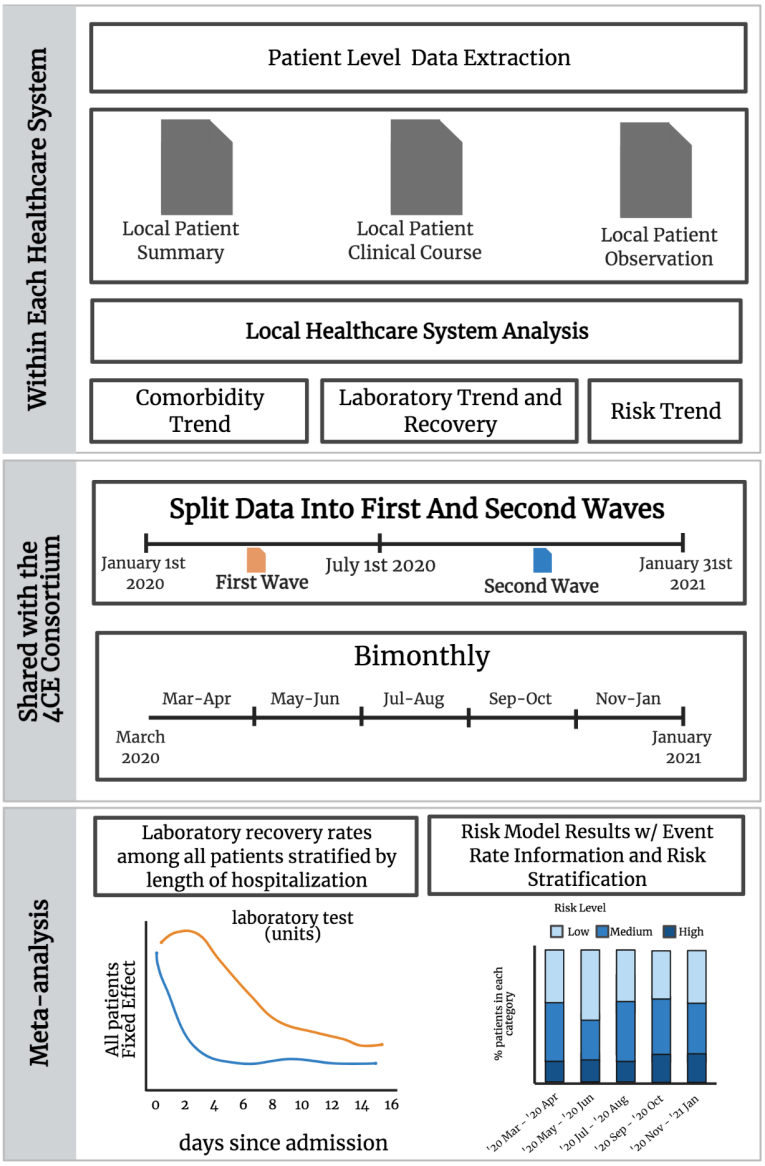
Supplementary eFigure 6. AUC of the Cox regression model for mortality risk prediction (excluding Italy).

Supplementary eFigure 7: Country-level risk model results w/ event rate information and risk stratification (excluding Italy).

eTable 1: Participating healthcare systems.The 170 US Veterans Affairs (VA) hospitals were grouped into 5 regional healthcare systems [1].

Healthcare system	Acronym	Country	City	Hospitals	Beds	Inpatient discharges/ year
Assistance Publique - Hôpitaux de Paris	APHP	France	Paris	39	20 098	1 375 538
Beth Israel Deaconess Medical Center	BIDMC	USA	Boston, MA	1	673	40 752
Bordeaux University Hospital	FRBDX	France	Bordeaux	3	2 676	130 033
Hospital Universitario 12 de Octubre	H12O	Spain	Madrid	1	1 256	45 035
ICSM Hospitals	ICSM	Italy	Pavia/Milan/Lumezzane/Brescia	3	775	12 344
Mass General Brigham (Partners Healthcare)	MGB	USA	Boston, MA	10	3 418	163 521
Northwestern University	NWU	USA	Chicago, IL	10	2 234	103 279
University of California, LA	UCLA	USA	Los Angeles, CA	2	786	40 526
University of Kansas Medical Center	KUMC	USA	Kansas City, KS	1	794	54 659
University of Freiburg, Medical Center	UKFR	Germany	Freiburg	1	1 660	71 500
University of Michigan	UMICH	USA	Ann Arbor, MI	3	1000	49 008
University of Pennsylvania	UPENN	USA	Philadelphia, PA	5	2 469	118 188
University of Pittsburgh	UPITT	USA	Pittsburgh, PA	39	8 085	369 300
VA North Atlantic	VA1	USA		49	3 594	151 075
VA Southwest	VA2	USA		29	3 115	156 315
VA Midwest	VA3	USA		39	2 686	145 468
VA Continental	VA4	USA		24	2 110	113 260
VA Pacific	VA5	USA		29	2 296	114 569
			Total	288	59 725	3 254 370

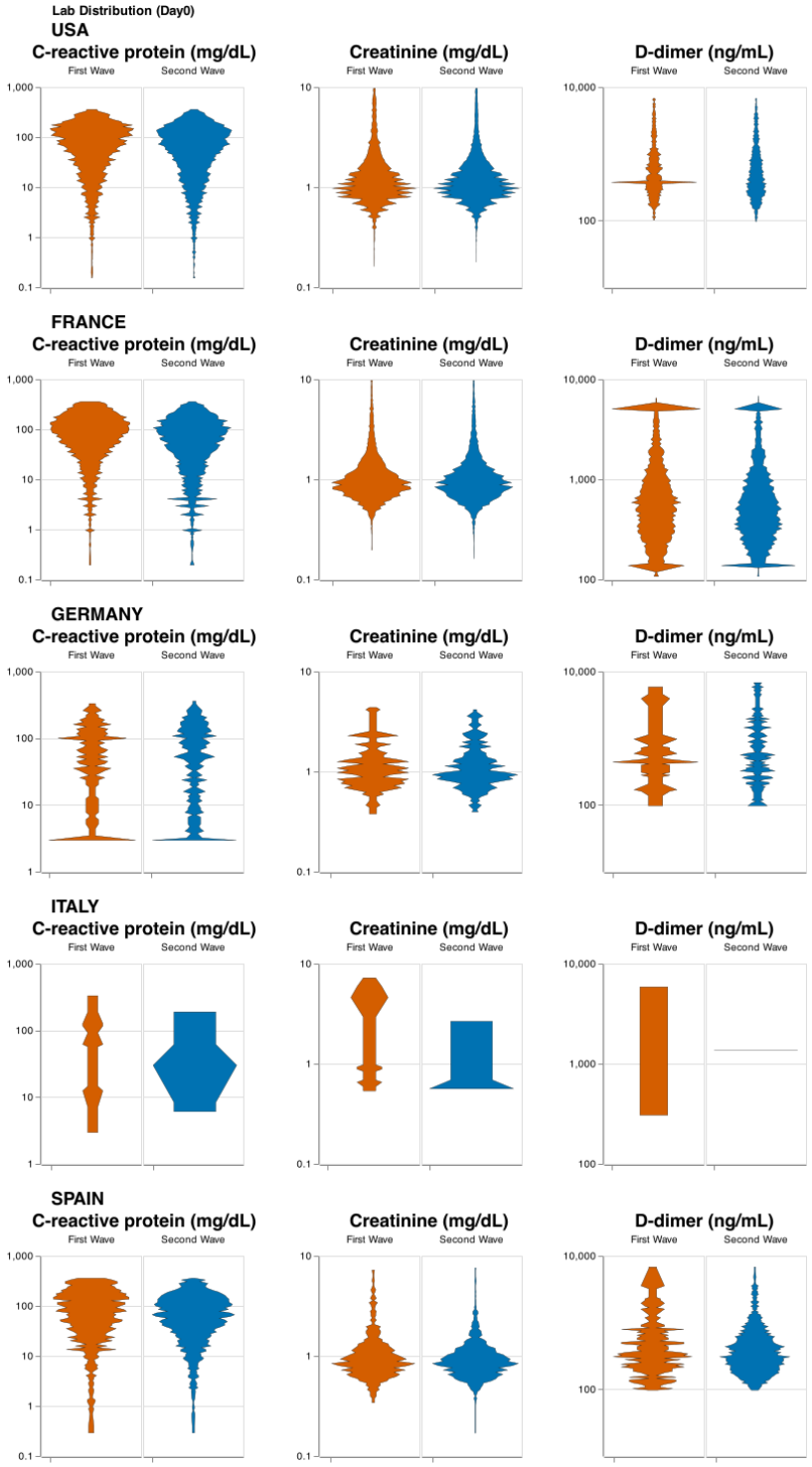
eFigure 1.Schematic of the federated EHR-based study involving healthcare systems from five countries. (created with BioRender.com)



Remark: The hospitalization rate over time tends to differ across regions and across countries, in part due to heterogeneity in a wide range of regional factors including community morbidity and local social distancing policy. This results in different relative sample sizes across healthcare centers over time. To ensure that the temporal trends in clinical presentations summarized via meta-analysis combining all healthcare centers are not driven by the temporal change in the relative sample sizes, we used the same weight for each healthcare center across different calendar months.

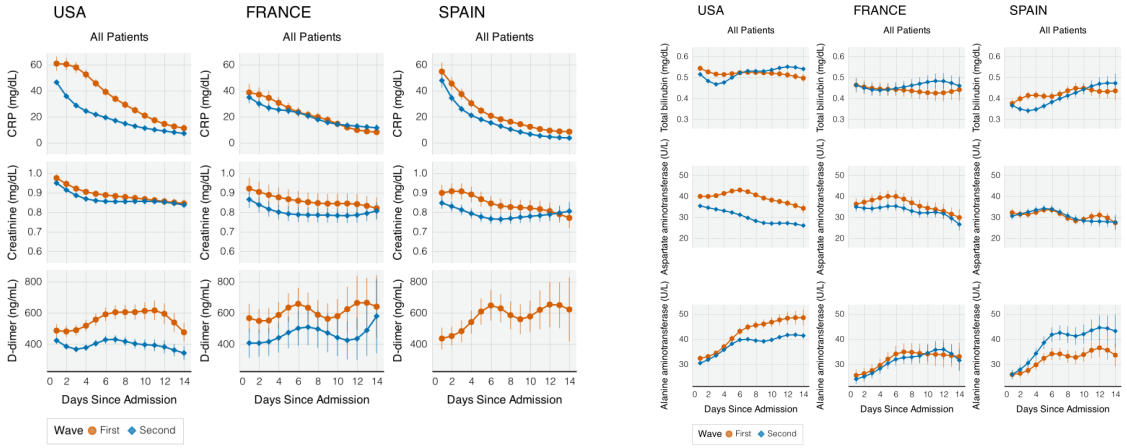
eFigure 2.Country-level demographic shifts.

eFigure 3. Country-level Distribution of laboratory values at admission. The Italy site had a relatively low percentage of patients with laboratory measurements which may have led to less precise estimates in these laboratory changes.

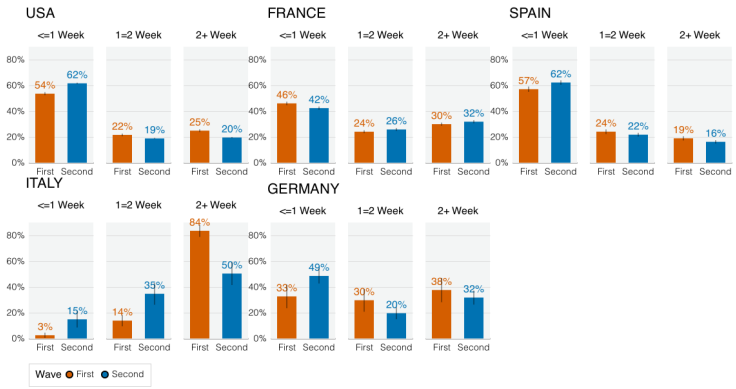


eFigure 4. Patient-level laboratory recovery rate. (a) country-level changes in the recovery rates of laboratory measures (excluding Germany and Italy due to the small number of patients with longitudinal laboratory measurements available); (b) distribution of length of hospital stay among patients admitted in the first wave and in the second wave

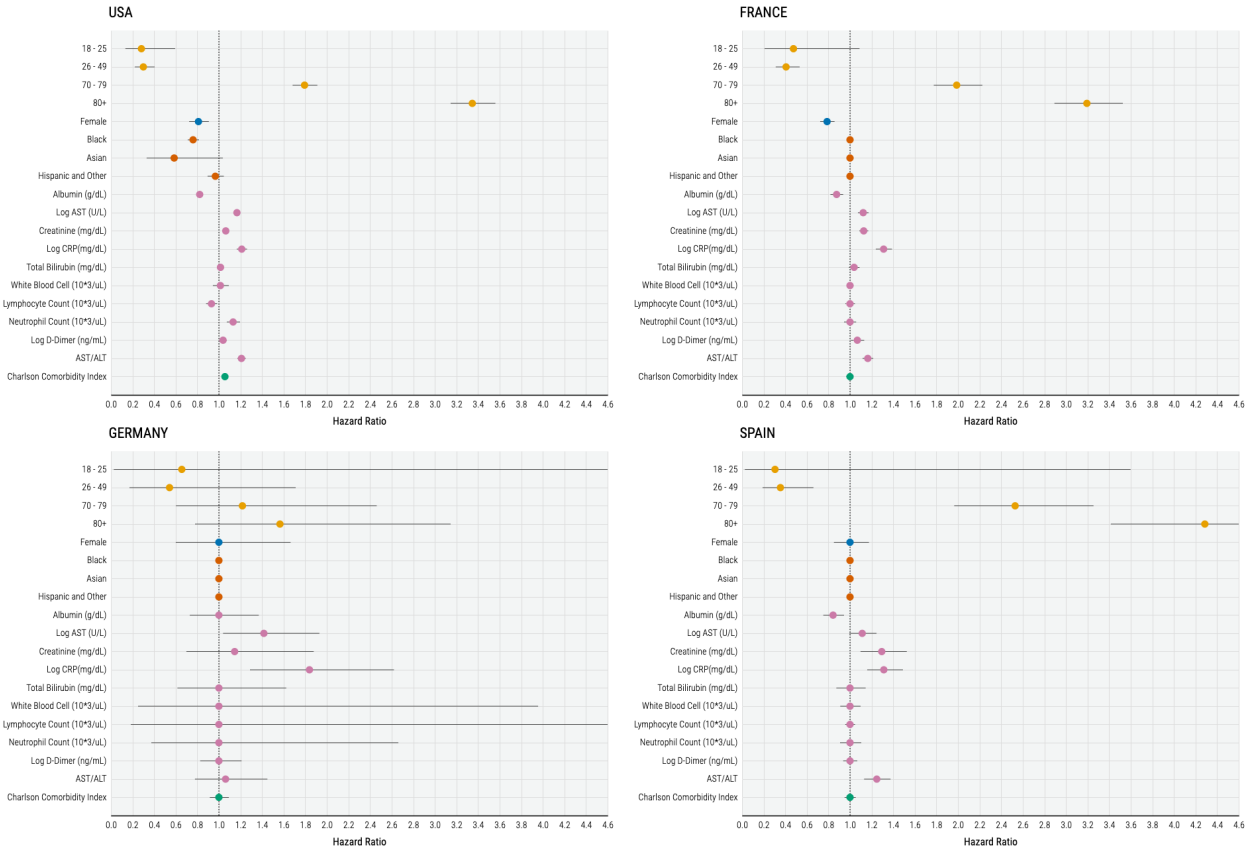
(a) country-level changes in the recovery rates of laboratory measures



(b) Distribution of length of hospital stay among patients admitted in the first wave and in the second wave

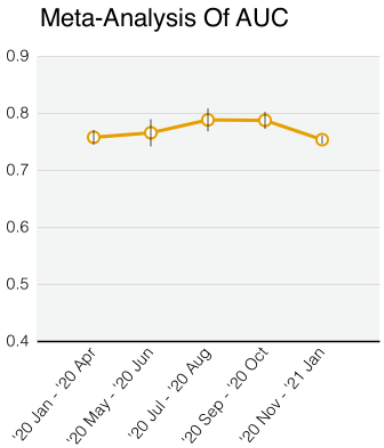


eFigure 5. Hazard ratio of the Cox model for mortality risk prediction (excluding Italy).

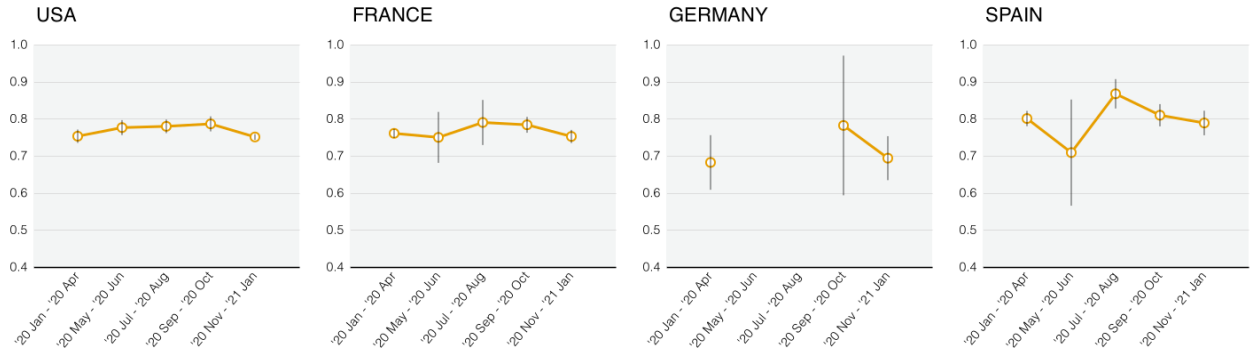

USA
FRANCE
GERMANY
SPAIN
18 - 25
26 - 49
70 - 79
80+
Female
Black
Asian
Hispanic and Other
Albumin (g/dL)
Log AST (U/L)
Creatinine (mg/dL)
Log CRP(mg/dL)
Total Bilirubin (mg/dL)
White Blood Cell (10*3/uL)
Lymphocyte Count (10*3/uL)
Neutrophil Count (10*3/uL)
Log D-Dimer (ng/mL)
AST/ALT
Charlson Comorbidity Index
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6
Hazard Ratio

eFigure 6. AUC of the Cox regression model for mortality risk prediction (excluding Italy).

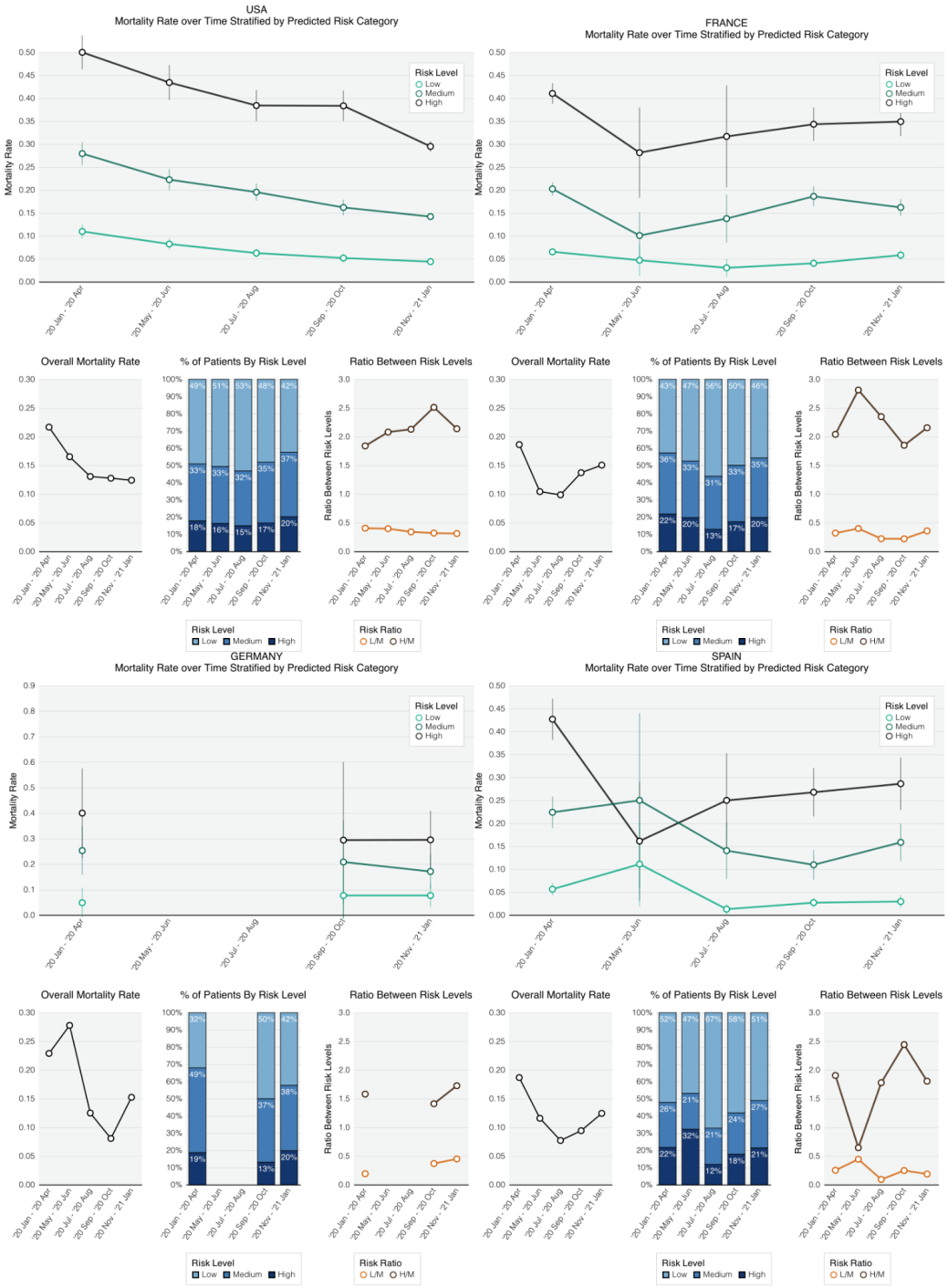
(a) Meta-analysis over all countries.



(b) Country-level AUC over time. AUC was not reported for May–June 2020, and July–August 2020 in Germany due to small counts of death occurring during these months.



eFigure 7. Country-level risk model results w/ event rate information and risk stratification (excluding Italy).



1. Jones AL, Pettey WBP, Carter ME, Brignone E, Redd A, Suo Y, et al. Regional Variations in Documentation of Sexual Trauma Concepts in Electronic Medical Records in the United States Veterans Health Administration. AMIA Annu Symp Proc. 2019;2019: 514–522.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	8 8
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10
		(*b*) Report category boundaries when continuous variables were categorized	8-10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.