Side-effects of COVID-19 on patient care: An INR story

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Key Words: COVID-19, INR, health care access
Short Title: Impact of COVID-19 on INR

ABSTRACT

Background: Numerous studies have documented reduced access to patient care due to the COVID-19 pandemic including access to a diagnostic or screening tests, prescription medications, and treatment for an ongoing condition. In the context of clinical management for venous thromboembolism, this could result in suboptimal therapy with warfarin. We aimed to determine the impact of the pandemic on utilization of International normalized ratio (INR) testing and the percentage of high and low results.

Methods: INR data from 11 institutions were extracted to compare testing volume and the percentage of INR results ≥3.5 and ≤1.5 between a pre-pandemic period (January-June 2019, period 1) and a portion of the COVID-19 pandemic period (January-June 2020, period 2). The analysis was performed for inpatient and outpatient cohorts.

Results: Testing volumes showed relatively little change in January and February, followed by a significant decrease in March, April and May, and then returned to baseline in June. Outpatient testing showed a larger percentage decrease in testing volume compared to inpatient testing. At 10 of the 11 study sites we observed an increase in the percentage of abnormal high INR results as test volumes decreased, primarily among outpatients.

Conclusion: The COVID-19 pandemic impacted INR testing among outpatients which may be attributable to several factors. Increased supratherapeutic INR results during the pandemic period when there was reduced laboratory utilization and access to care is concerning because of the risk of adverse bleeding events in this group of patients. This could be mitigated in the future by offering drive through testing and/or widespread implementation of home INR monitoring.

IMPACT STATEMENT

Restrictions and distancing policies during the COVID-19 pandemic reduced access to healthcare services. We found that the shutdown was associated with a decrease in testing and an increase in abnormal results for a commonly utilized and clinically actionable laboratory test (INR). This trend was consistent at laboratories across North America. These results provide insight into the in the side effects of reduced access to routine care and can inform planning to improve care during future periods with reduced access to care.

INTRODUCTION

Venous thromboembolism (VTE) affects up to an estimated 600,00 patients per year in the United States alone.(1) Various antithrombotic drugs are a component of treatment for VTE. Among these, warfarin is a commonly prescribed drug which requires laboratory monitoring. The dosage and administration of warfarin is adjusted based on the patient's International Normalized Ratio (INR).(2, 3) The INR target range and duration of therapy varies depending on the indication for treatment; however, a target INR of 2-3 is generally recommended.(2, 3) There are other clinical indications for warfin therapy, including prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation, cardiac valve replacement, and reduction of the risk of death or recurrent thromboembolic events associated with myocardial infarction. (please add reference using EndNote) The target INR varies depending on the indication for anticoagulation.

Subtherapeutic and supratherapeutic INR response to warfarin pose risks to patients' health. A subtherapeutic INR (<2.0) portends increased risk of thrombosis, whereas adverse bleeding events are the primary concern with a supratherapeutic INR (>4.0). Achieving the optimal target INR is a challenge due to patient compliance, drug-drug interactions, and pharmacogenomic factors, among others.(2, 3) Maintaining a target INR requires longitudinal monitoring because of variability in these factors over time. Many institutions have protocols for how to adjust dosing based on INR results. Numerous strategies may be used to guide warfarin therapy including inpatient and outpatient anticoagulation management services, computer-aided dosing decision support, and patient self-management.(4)

According to the National Center for Health Statistics, up to 38% of individuals surveyed using The Research and Development Survey indicated reduced access to care due to the COVID-19 pandemic.(5) Up to 6.4% of respondents indicated reduced access to a diagnostic or screening tests, 3.2% experienced reduced access to prescription medications, and 6.2% reported reduced access to treatment for an ongoing condition. In the context of clinical management for VTE, this could result in

suboptimal therapy with warfarin. We aimed to determine the impact of the COVID-19 pandemic on utilization of INR testing and the percentage of high and low results.

METHODS

INR data from 11 institutions were extracted to compare testing volume and the percentage of supratherapeutic results between a pre-pandemic period (January-June 2019, period 1) and a portion of the COVID-19 pandemic period (January-June 2020, period 2). The set of institutions was a convenience sample selected with the goal to have a broad geographical distribution and a sufficient sample size to show broad patterns in testing. Ten of the 11 laboratories obtained data by querying the laboratory information system (LIS) and one laboratory queried the electronic health record. Each laboratory preprared a summary (number of results by month, stratified by patient type and result category (normal vs abnormal) and submitted the resulting tables to the authors at the University of Utah (LP, RLS) who compiled the results into a single database and performed the analysis. Both lab-based and point-of-care test results were included. We determined the median and interquartile range (IQR) for monthly INR test volume and percent of supratherapeutic INR results (INR results greater than or equal to 3.5) and INR results less than or equal to 1.5. These cutoffs were chosen to select for INR results that may be clinically actionable.

We determined the impact of the pandemic by comparing the testing volumes and the percentage of supratherapuetic results for each month in period 1 and period 2. We calculated the percent change in testing volume (ΔV) and the change in results (ΔA) above and below the cutoffs for each month during the pandemic period at each study site relative to the same month from 2019. We also calculated the median percentage change in volume (ΔV_m) and median percentage change in results (ΔA_m) over all locations. We calculated these statistics (ΔV_m and ΔA_m) for three cohorts: all patients, inpatients and outpatients.

Data from all sites were aggregated and five-point summaries were calculated (minimum, 25th percentile, median, 75th percentile, maximum) for each statistic by month for each cohort. The monthly change was visualized by creating box plots of the percent change in volume and results by month. We also tested for a relationship between ΔV and ΔA using hierarchical regression with location as a random effect and plotted the relationship between ΔV and ΔA for each site. In hierarchical regression, one assumes that there is a linear relationship between variables (ΔV and ΔA) for each site, but that the relationship can vary by site. This type of regression analysis determines whether there is a broad relationship between the variables of interest (e.g. is the relationship between ΔV and ΔA generally positive or negative?). This method of analysis was chosen because we would expect results within a hospital to be correlated more than results across hospitals.

Statistical analysis was performed using Stata 16.2 (Stata Corp, LLP). Hierarchical regression was performed using the *mixed* command as implemented by Stata.

RESULTS

Characteristics of Participating Institutions: Eleven institutions participated in the study (Table 1). The institutions were dispersed geographically across the United States (N=9) and Canada (N=2). The median monthly volume of INR testing during the pre-pandemic period was 8780 (IQR: 5423 – 12060) for all patients, 5127 for inpatients (IQR: 3219-8505), and 3237 (IQR: 1931 – 7021) for outpatients. The median percentage of low INR results (INR ≤ 1.5) in the pre-pandemic period was 71% (IQR: 65-81) for all patients, 71% (IQR: 67 - 80) for inpatients, and 70% (IQR: 31 – 76) for outpatients. The median percentage of high abnormal INR results (INR ≥ 3.5) in the pre-pandemic period was 3.4% (IQR: 2.0 – 4.0) for all patients, 2.9% (IQR: 2.0 – 3.5) for inpatients, and 4.1% (IQR: 2.6 – 6.5) for outpatients.

Impact of COVID on Testing Volumes. Testing volumes showed relatively little change in January and February, followed by a significant decrease in March, April and May, and then returned to baseline in June (Supplementary Table 1 A, Figure 1, Figure 2). Outpatient testing showed a larger

percentage decrease in testing volume compared to inpatient testing. During March, April and May, the median decrease in inpatient testing volumes were 17%, 30% and 17% respectively. Outpatient testing volumes decreased by 23%, 39%, and 28% during March, April, and May respectively.

Impact of COVID on High Abnormal INR Results (INR ≥ 3.5): The number of high abnormal INR results showed relatively little change among inpatients. Among outpatients, high INR results increased by 27% in April and 20% in May (Supplemental Table 1C, Figure 1).

We tested for a relationship between the percent change in testing volume (ΔV) and the percent change in abnormal INR results (ΔA) among outpatients. At 10 of the 11 study sites we observed an increase in the percentage of abnormal INR results as test volumes decreased (Figure 3). This relationship varied by site but, on average, there was a 0.65% increase in high results for every 1% decrease in testing volume ($p < 0.0005$). Although the relationship was significant among outpatients, there was no significant relationship between the percentage change in testing volume and the percentage change in high abnormal results among inpatients (p=0.66).

We observed some outliers in volume (Figure 1) and percentage change in abnormal results (Figure 2) but were not able to determine the cause. The no single institution was a consistent outlier (Supplementary Figure 3).

Impact of COVID on Low INR Results (INR ≤1.5): There was very little change in the percentage of patients with low INR values (Figure 2, Supplementary Table 1B). Among inpatients, the percentage change in low results ranged from 0.4 to 1.5 percent. Among outpatients, the percentage change ranged from -6.6 to 3.8 percent. Among outpatients, the percentage of low INR results increased by 0.2% for every 1% decrease in testing volume ($p< 0.0005$). Among inpatients, there was no association between the percentage change in testing volume and the percentage change in low results (p=0.80).

DISCUSSION

In this study we assessed the impact of the COVID-19 pandemic on INR testing volumes and high and low INR results in both inpatients and outpatients across 11 different healthcare institutions in North America. We observed a large reduction in INR test volumes during March, April, and May 2020, corresponding to community lockdowns enacted across the United States and Canada during the early months of the pandemic. A greater reduction in INR test volumes occurred in the outpatient setting, with a corresponding increase in the percent of abnormally high INR results. A recent study contradicts our findings, reporting a net increase in PT/INR testing but did not partition its findings to inpatient versus outpatient testing.(6) Presumably the increased utilization of INR testing was in an inpatient cohort. Our findings are important and may inform healthcare institutions of opportunities for improvement during future pandemic-associated lockdowns. We believe several aspects of our study warrant further discussion.

The overall reduction in INR testing we demonstrated during the pandemic period is likely attributable to several factors. Many hospitals and clinics canceled elective procedures and routine visits in anticipation of a surge of patients with COVID-19. We speculate this resulted in a reduction of routine pre-procedural INR testing and screening INRs among healthy outpatients. The reduction in INR test volume was smaller among inpatients, potentially due to the fact that patients necessitating hospitalization require more frequent testing due to their acute illnesses and concern for coagulopathy complicating COVID-19 infection(7, 8).

We observed a decrease in INR testing volume in both inpatients and outpatients. This was consistent across all hospitals (Supplementary Figure 1). The decrease in volume was most likely due to reduced monitoring; however, there are other potential explanations. For example, a reduction in volume could be caused by a disruption of service (e.g., due to a covid outbreak amon laboratory staff). We conducted a poll across all contributing laboratories and found that none had a disruption of service during the pandemic period. Testing volume could have decreased due to efforts to switch patients to

direct oral anticoagulants that do not require monitoring. We were unable to collect data on prescribing patterns from all contributors but we did perform an audit at the University of Utah and found that prescribing patterns were unchanged. We also found that testing volumes for a range of tests showed a similar pattern to INR. Thus, it is unlikely that the decrease was due to a change in prescribing patterns. The testing pattern showed a sharp decrease followed by a fast return to normal testing volume so it is unlikely that the decrease in testing was due to covid associated mortality.

We observed an increase in the proportion of high INR results among outpatients during the pandemic period. This observation may reflect a shift in the study population resulting from selection bias for patients prescribed warfarin who require frequent INR testing. More worrisome is the possibility that there was voluntary avoidance of the healthcare system by patients due to a fear of contagion. This fear may have influenced healthcare providers and clinic staff as well, leading to impaired acess to testing due to closed medical practices or pharmacists working remotely. Considering the majority of patients on warfarin are outpatients, avoidance of testing, or reduced access to testing, would disproportionately affect patients on warfarin. Although this study is not designed to correlate our findings with patient outcomes, increased supratherapeutic INR results during the pandemic period when there was reduced laboratory utilization and access to care is concerning because of the risk of adverse bleeding events in this group of patients.

Our study has several strengths and weaknesses. We believe our results are widely generalizable based on the broad sample of both inpatient and outpatient INR results from academic and non-academic practice settings across a wide geographic area in the United States and Canada. The lack of baseline patient characteristics may be viewed as a limitation of the study, albeit a small limitation, as the increased percentage of supratherapeutic INR results with decreased test volumes was consistent across all study sites except one. We were unable to determine why the data from this institution show the opposite pattern. The inability to identify which patients were prescribed warfarin or those with

liver disease is another limitation. This would have allowed us to identify abnormally low INRs in warfarin patients, and to further differentiate the abnormally high INR cohort. Although our results demonstrate a large reduction in laboratory testing volumes, we can only speculate whether this is due to voluntary avoidance of the healthcare system by patients or impaired access to care. It is unknown if the reduction in testing could be attributable to patients being transitioned from warfarin to a different anticoagulant that does not require laboratory monitoring, or attributed to death in patients requiring anticoagulation with a diagnosis of COVID-19. We are unable to correlate this data with SARS-CoV-2 infection status in any patients. Furthermore, COVID-19 can induce coagulopathy that requires specialized coagulation laboratory monitoring to prevent the sequelae of thrombosis or disseminated intravascular coagulation(9, 10). Therefore it is pertinent to evaluate coagulation monitoring practices during the pandemic. We selected cutoffs for abnormal results that are applicable to the majority of patients but would not be applicable to all patients. This is a potential limitation; however, it was unlikely to have a significant impact on the conclusions.

Regardless of the limitations, one may conclude the COVID-19 pandemic impacted INR testing among outpatients. This information may be useful for planning considerations prior to the next pandemic-associated lockdown and other events that may reduce access to healthcare. Ideas for ways to mitigate this for patients taking warfarin include offering drive through testing and/or widespread implementation of home INR monitoring.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

M.E. Lyon, provision of study material or patients; R.L. Schmidt, statistical analysis.

Employment or Leadership: L.N. Pearson, University of Utah, ARUP Laboratories; D.N. Greene, *The Journal of Applied Laboratory Medicine*, AACC; A.B. Chambliss, *The Journal of Applied Laboratory Medicine*, AACC; D. French, *The Journal of Applied Laboratory Medicine*, AACC.
Consultant or Advisory Role: D.S. Herman, Roche Diagnostics.
Stock Ownership: J.A. SoRelle, Myriad Genetics.
Honoraria: None declared.
Research Funding: None declared.
Expert Testimony: None declared.
Patents: None declared.

Role of Sponsor: No sponsor was declared.

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Table 1: Characteristics of Participating Institutions. The table shows the average total (inpatient and outpatient) monthly testing volume for the international normalized ratio (INR) test and the average percent of the total test results that were below 1.5 and above 3.5.

Institution	**Baseline INR Testing (2019 average)**		
	Monthly Volume	**Percent Below 1.5**	**Percent Above 3.5**
University of Saskatchewan	12273	62.7	3.8
University of Utah	5310	70.4	3.9
University of CA, San Francisco	8374	76.1	1.9
Los Angeles County USC Medical Center	9526	82.7	1.7
McMaster University	3532	86.7	1.6
University of Iowa	6135	70.4	3.8
Kaiser Permanente, Washington	8828	18.3	6.7
Geisinger	18760	48.7	5.5
Washington University, Saint Louis	11186	67.7	3.4
University of Texas Southwestern Medical Center	5083	64.6	3.8
Univ of Penn	26430	80.5	2.5

Figure Legends

Figure 1: Change in the Relative Testing Volume and Relative Percentage of High INR Results by Month. Relative change was measured as 2020 results relative to 2019. INR results ≥ 3.5 were categorized as abnormal. Each month represents results from 11 sites. The white line in the box indicates the median and the length of the box indicates the interquartile range. Dots indicate outliers. Numerical values corresponding to the figure are detailed in Supplemental Table 1.

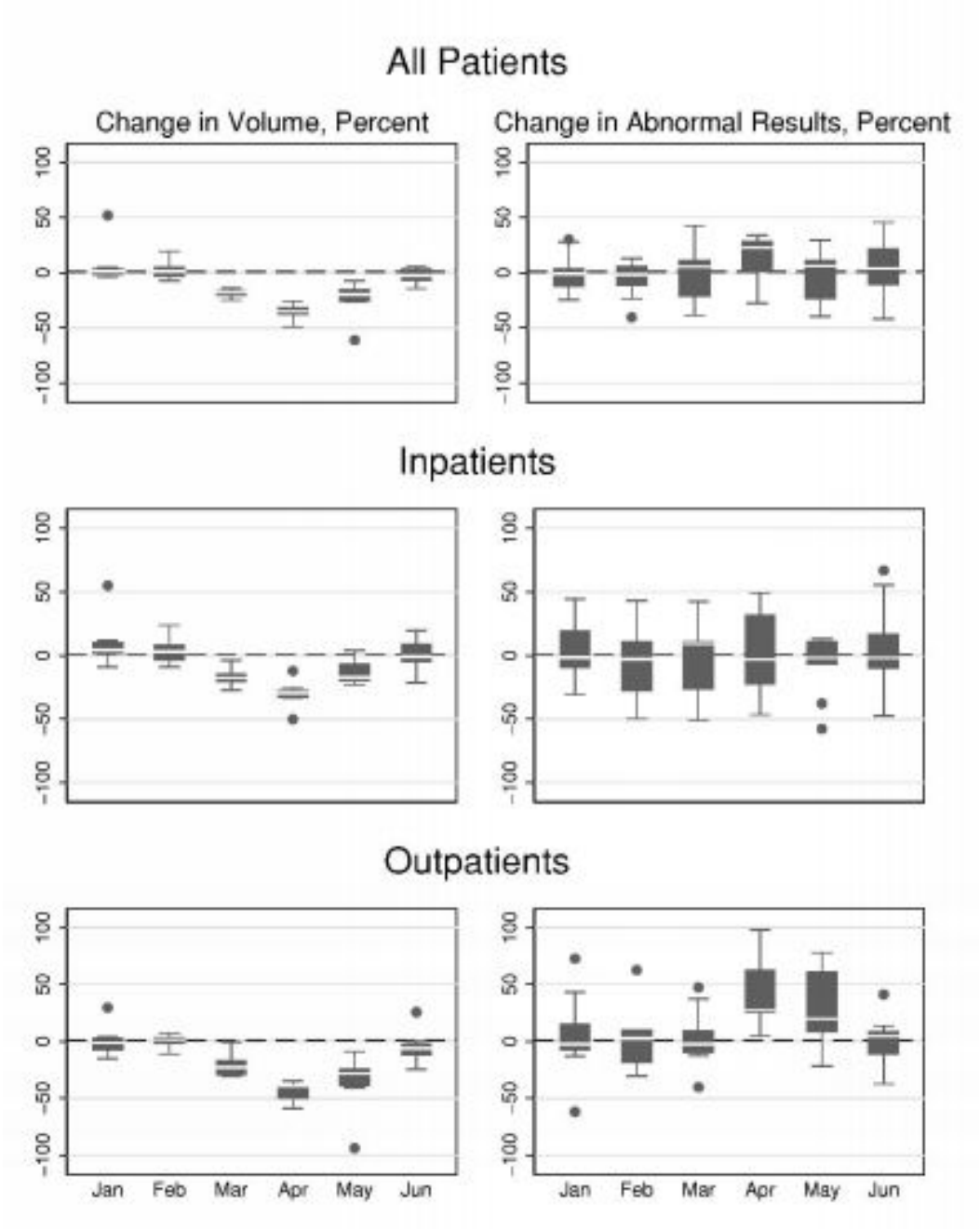

Figure 2: Change in the Relative Testing Volume and Relative Percentage of Low (≤ 1.5) **INR Results by Month**. Relative change was measured as 2020 results relative to 2019. Each month represents results from 11 sites. The white line in the box indicates the median and the length of the box indicates the interquartile range. Dots indicate outliers. Numerical values corresponding to the figure are detailed in Supplemental Table 1.

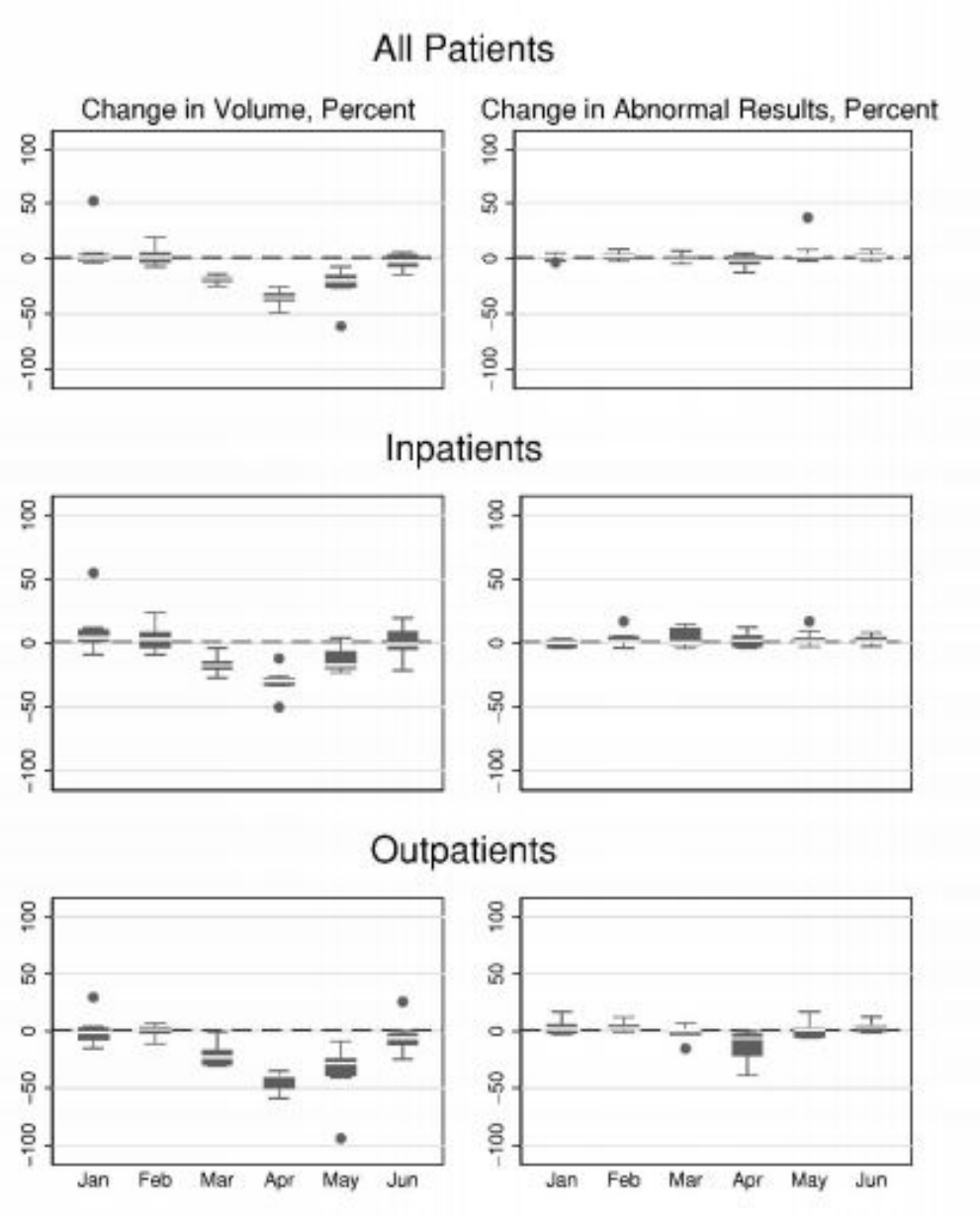

Figure 3: Relationship between the Percent Change in Testing Volume and Percent Change in High INR (INR≥ 3.5) Results (2020 relative to 2019) for Outpatients by Location. Each line shows the relationship between the percentage change in abnormal results, ΔA, and the percentage change in INR testing volume, ΔV, for one location over six months. The percentage change between 2019 and 2020 was calculated by month from January to June. The lines represent the best fit line (linear regression) for each hospital.