Assessing Provider Utilization of COVID-19 Inflammatory Marker Trends in Hospitalized Patients and Implications in Optimizing Value-Based Care During a Pandemic

Praveen Subramanian, D.O.[1], Lucy Stun, Pharm.D.[2], Kellie Wark, M.D.[3], Nathan C. Bahr, M.D.[3], Wissam El Atrouni, M.D.[3], Lewis Satterwhite, M.D.[4], Maharshi Bhakta, M.D.[1], Fred Plapp, M.D., Ph.D.[5], Jessica R. Newman, D.O.[3]
University of Kansas Medical Center, Kansas City, KS
[1]Department of Internal Medicine
[2]Department of Inpatient Pharmacy
[3]Department of Internal Medicine, Division of Infectious Diseases
[4]Department of Internal Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine
[5]Department of Pathology and Clinical Laboratory Medicine

ABSTRACT

Introduction. Numerous inflammatory markers may serve a role in prognostication of patients hospitalized with COVID-19 infection. Early in the pandemic, our health system created an admission order set which included daily d-dimer, c-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin. Given more available outcomes data, limiting standing order of labs that do not affect daily management could result in significant cost savings to the health system without adverse patient outcomes. The purpose of this study was to determine ordering and utilization patterns of inflammatory markers by physicians caring for patients hospitalized with COVID-19 infection.

Methods. An anonymous 10-question survey was distributed to 125 physicians (Infectious Disease, Hospitalist, Pulmonary and Critical Care faculty). Responses were tallied and values greater than 50% were identified as the majority of the surveyed group.

Results. Of the 125 physicians surveyed, 77 (62%) responded. A total of 57.1% (44/77) of physicians reported ordering daily inflammatory markers for 3 - 10 days from admission. Another 31.2% (24/77) ordered markers until clinical improvement or hospital discharge. D-dimer was used for care decisions by 83.1% (64/77) of respondents; 93.8% (60/64) of those reported utilizing it in determining anticoagulation dose. CRP was used by 61% (47/77) of physicians to help identify a secondary infection or determine steroid dose or duration. LDH and ferritin were not used for management decisions by the majority of physicians. Inflammatory markers were not used routinely after isolation precautions had been discontinued, even when ongoing care required mechanical ventilation.

Conclusions. Of the markers studied, both d-dimer and CRP were considered useful by most respondents. LDH and ferritin were used less frequently and were not considered as useful in guiding medical decision making. Discontinuation of standing daily LDH and ferritin orders is believed to have potential to result in cost savings to the health care system with no adverse patient outcomes.

INTRODUCTION

In December 2019, a novel coronavirus was described in Wuhan, China and quickly spread throughout the world. By the end of January 2020, the World Health Organization declared the outbreak a Public Health Emergency of International Concern.[1] According to the Johns Hopkins Coronavirus Resource Center, there have been a total 397 million cases worldwide, including 5.75 million deaths as of February 8, 2022.[2] Early in the pandemic, risk factors for progression to severe disease were identified by analyzing trends in hospitalized patients including age, hypertension, diabetes, body mass index (BMI), and race. In addition, elevations in numerous inflammatory markers were found to be risk factors for disease severity.[3] Laboratory markers associated with critical illness included lymphocytopenia, thrombocytopenia, elevated c-reactive protein (CRP), elevated transaminases, decreased creatinine clearance, elevated ferritin, elevated lactate dehydrogenase (LDH), elevated serum amyloid A, and elevated d-dimer.[4,5]

Using a retrospective cohort analysis published in September 2020, researchers at Johns Hopkins developed a COVID-19 Inpatient Risk Calculator.[3] When laboratory results and patient data are applied to the calculator, death and progression to severe disease can be predicted. Two predominant risk factors have direct implications in therapy, d-dimer and a requirement for supplemental oxygen. The RECOVERY Trial demonstrated improved 28-day mortality when administering dexamethasone to COVID-19 patients requiring supplemental oxygen compared to placebo.[6] Patients with elevated d-dimer plus a sepsis-induced coagulopathy score ≥ 4 have improved 28-day mortality when given low molecular weight heparin versus no heparin product.[7] In a randomized, controlled, open-label trial, the RECOVERY Collaborative Group identified tocilizumab as having improved 28-day mortality in patients with hypoxia and CRP > 7.5 mg/dL.[8] Clear evidence regarding the roles of ferritin and LDH in guiding COVID-19 therapy were not available.

At The University of Kansas Health System (TUKHS; Kansas City, KS), CRP, ferritin, LDH, and d-dimer were added to the inaugural COVID-19 admission order set as inflammatory markers of interest based on information related to clinical outcomes in patients with COVID-19 available at the time. This order set was designed specifically for admitting patients with SARS-CoV-2 positive polymerase chain reaction (PCR) to guide initial monitoring and management. The order set included options for daily monitoring of CRP, ferritin, LDH, and d-dimer but had no expiration date based on clinical status (indefinite until death or hospital discharge). If a physician felt there was no longer need for inflammatory marker trending, they would have to discontinue the orders manually. TUKHS operates with a closed ICU model where intensivists act as the primary physician for patients meeting ICU admission criteria. Hospitalists acted as the primary physician for most general internal medicine COVID-19 patients admitted to telemetry and general medicine wards. Consultation with Infectious Diseases or Pulmonary services was at the discretion of the primary

service and not a requirement. While there are implications for patient management with d-dimer results, the roles of the other markers, outside of risk stratification, are less clear.

From March 1, 2020 to February 6, 2021, TUKHS admitted 2,369 patients with COVID-19 with an average length of stay of 7.7 days resulting in a total of 18,241 patient days. The cost for reagent and labor on average per test for d-dimer, CRP, LDH, and ferritin is $7.55 at our institution. This represented approximately $551,000 spent on inflammatory markers for COVID-19 patients since the beginning of the pandemic at TUKHS.

The study aim was to use survey responses from physicians most frequently assigned to care for patients with COVID-19 to determine if daily trends in d-dimer, LDH, ferritin, and CRP guided daily management in patients hospitalized with COVID-19. Of particular interest were steroid duration and dose, level of anticoagulation (therapeutic versus prophylactic), and workup of potential secondary infection. Secondarily, we aimed to see if "recovered" status as determined by Infection Prevention and Control (IPAC) professionals altered the perceived frequency of COVID-19 inflammatory marker ordering. Finally, we sought to determine if there were potential laboratory cost savings to be obtained by comparing the self-reported ordering patterns of the tests in question to the self-perceived utility of these tests in patient care.

METHODS

An anonymous and voluntary 10 question yes/no/open-ended response survey utilizing SurveyMonkey®, an online survey development cloud-based software, was distributed to faculty within infectious diseases, intensive care, and hospital medicine who practiced at TUKHS in December 2020 (Figure 1). This staff was selected given they provided the majority of daily care to patients admitted with COVID-19 infection. The survey was closed after one month. The results of the survey were tabulated for each question. An open-ended response that qualified for multiple preselected categories was split accordingly. For example, for a respondent who used c-reactive protein for both steroid dosing and workup of a secondary infection, 0.5 votes were added to each category. In the case that an open response qualified for three categories, 0.33 votes were added to each category. Votes then were converted to percentages of all respondents. For purposes of evaluation of responses, options selected by greater than 50% of the surveyed population were considered to represent the majority of the respondents. This quality improvement project was approved by the University of Kansas Medical Center Human Subjects Committee prior to the distribution of the survey. The nature of the study and associated survey was exploratory. Patients were not involved directly in this study.

RESULTS

Of the 125 physicians surveyed, 14 were Infectious Disease faculty, 28 were Intensivists/Pulmonary consultants, and 83 were Hospitalists. Of those invited to participate, 62% (77/125) completed the survey (Table 1). The faculty responding were not required to document which division they represented. Most physicians checked inflammatory markers for at least three to five days of hospitalization; 30% (23/77) checked for 6 - 10 days and 18% (14/77) monitored until discharge

(Figure 2). In total, 57.1% (44/77) of respondents obtained inflammatory markers daily (Figure 3).

How often do you check COVID-19 inflammatory markers?	
How many days do you check COVID-19 inflammatory markers?	
Do you check COVID-19 Inflammatory markers on "recovered" patients who are actively requiring mechanical ventilation?	
Do you check COVID-19 Inflammatory markers on "recovered" patients who are actively requiring Heated High Flow Nasal Canula?	
Do you check COVID-19 inflammatory markers on "recovered" patients who are requiring supplemental oxygen via traditional nasal canula?	
Do you use d-dimer to change management of	
	Steroid duration or dose
	Anticoagulation
	Workup of secondary infection
	Other (please explain)
Do you use ferritin to change management of	
	Steroid duration or dose
	Anticoagulation
	Workup of secondary infection
	Other (please explain)
Do you use c-reactive protein to change management of	
	Steroid duration or dose
	Anticoagulation
	Workup of secondary infection
	Other (please explain)
Do you use LDH to change management of	
	Steroid duration or dose
	Anticoagulation
	Workup of secondary infection
	Other (please explain)
Do you think that removing the check-boxes for standing COVID-19 inflammatory markers (essentially requiring a provider to place the order on an as needed basis) will negatively impact patient care?	

The survey was distributed via an email link to 125 physicians who actively participated in the care of patients infected with COVID-19. Preceding the survey was a short disclaimer. "The following is a 10 question multiple choice survey. Please assume that all questions are regarding patients who have a positive COVID-19 PCR and symptoms on admission unless explicitly stating otherwise. COVID-19 inflammatory markers include d-dimer, ferritin, lactate dehydrogenase (LDH), and c-reactive protein (CRP). "Recovered" is the designation that Infection Prevention and Control gives to patients who no longer need isolation."

Figure 1. COVID-19 Inflammatory Marker Usage Survey.

Table 1. Survey demographics.

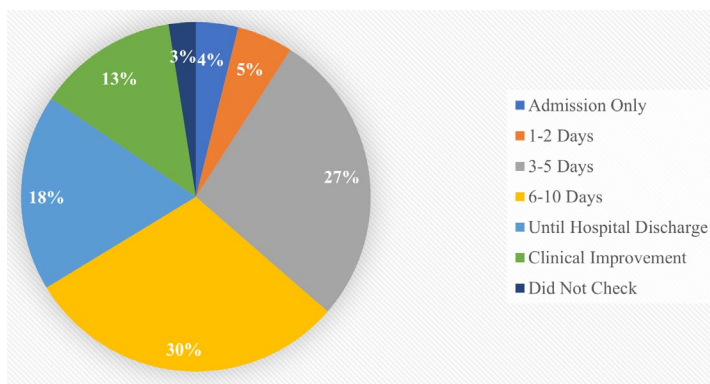| Faculty division	Number of physicians
Infectious Disease faculty	14
Critical Care faculty	28
Hospitalist	83
Total	**125**
Surveys completed	**77**
% Surveys completed	**62**

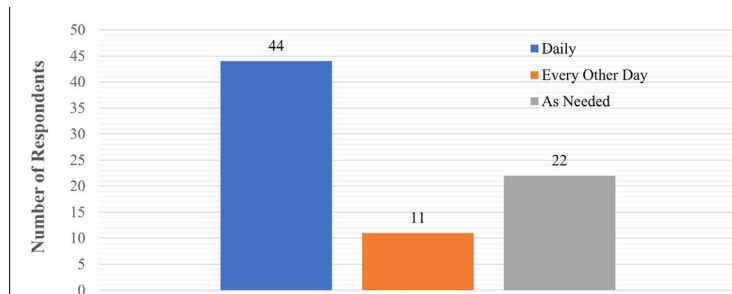Figure 2. Duration of COVID-19 Inflammatory marker monitoring.

Figure 3. COVID-19 inflammatory marker monitoring frequency.

D-dimer was utilized by 83.1% (64/77) of respondents for medical management decisions. Of the 83%, 93.8% (60/64) used d-dimer to determine dose of anticoagulation. Ferritin was not used regularly by 49.4% (38/77) respondents and used only for trending purposes in 2.6% (2/77). Of the remaining 46.8% (36/77) of providers who answered, 62% (22.33/36) used the ferritin level to determine steroid duration or dose and 31.5% (11.33/36) utilized ferritin in the workup of a secondary infection, respectively. Most providers (61%; 47/77) used CRP to make medical decisions, with 57.1% (26.83/47) of respondents using CRP to determine steroid duration or dose and 35.8% (16.83/47) reporting use in the workup of a secondary infection. Most physicians (59.7%; 46/77) did not use LDH to guide any therapy. One respondent deferred to answer how each inflammatory marker was utilized (Table 2).

Of the 77 survey respondents, 32 reported managing mechanically ventilated patients as part of their practice. Of those 32, 56.3% (18/32) did not check the aforementioned COVID-19 inflammatory markers in patients requiring mechanical ventilation and determined to be "recovering" by IPAC. Of the respondents managing patients requiring heated high flow nasal canula (53/77), 56.6% (30/53) reported checking inflammatory markers. In addition, 61% (47/77) of all respondents did not check inflammatory markers on "recovered" patients requiring supplemental oxygen by nasal cannula (Table 3).

When asked if changing the current COVID-19 admission order set would affect patient care negatively, 62.3% (48/77) reported that it would not, while 37.7% (29/77) felt that it was possible or that they were unsure. The concern that inadequate dosing of anticoagulation would be a result of not obtaining d-dimer leading to increased thromboembolic events was reported most frequently.

DISCUSSION

The COVID-19 pandemic has presented numerous challenges related to diagnostic testing, therapeutic development and implementation, vaccine development, and management of complications, amongst other issues. Through worldwide efforts, these processes have been expedited and improved in all areas. There is still a significant burden on hospital systems to manage hospitalized patients with severe symptoms from COVID-19. The abundance of case series, retrospective analyses, and prospective studies have helped to identify markers of inflammation and their association with prognosis.[3-5] A meta-analysis regarding the association of inflammatory markers in COVID-19 could not conclude that ferritin was correlated with severe disease.[9] While there is evidence supporting use of d-dimer to guide anticoagulation and CRP for tocilizumab administration, there is a limited role outside of prognostication for other markers.[8] Our survey suggested that most providers at our institution measure inflammatory markers on a daily basis for at least three to five days, with many checking for six to ten days or until discharge. Additionally, the survey suggested that physicians used inflammatory markers for trending inflammation, steroid dosing or duration, anticoagulation dosing, and workup of a secondary infection. In other responses, they were not being used at all. For respondents who felt there was a need to monitor multiple inflammatory markers, there was not a specific question to inquire about why they believed this practice was beneficial.

Most providers checked inflammatory markers daily for at least three to five days. This supported the practice of using the institution's COVID-19 admission order set via the electronic medical record, particularly given that most respondents (93.8%; 60/64) used d-dimer to assist in dosing of anticoagulation. Our institution adopted an algorithm that included d-dimer levels among other factors to determine anticoagulation dosage based on the published literature at the time.[7] Prior analysis showed that up to 25% of patients with COVID-19 requiring intensive care unit (ICU) level of care were diagnosed with venous thromboembolism (VTE).[10] Sequential autopsies on 26 COVID-19 patients performed at Mount Sinai Health System revealed that 42% of patients had either pulmonary embolism or VTE without clinical suspicion prior to their deaths. In addition, four of the 26 who had autopsies performed required therapeutic anticoagulation prior to admission for another condition. Although none of the patients previously on therapeutic anticoagulation had VTE on autopsy, there was evidence of microthrombi in two of the four.[11] Given the evidence supporting d-dimer's utility in anticoagulation dosing and mortality benefit with prophylactic anticoagulation, one could argue against checking d-dimer in the population who required therapeutic anticoagulation prior to admission. Our results suggested that physicians find utility in frequent monitoring of d-dimer. Although there is significant evidence of VTE being problematic in COVID-19, the exact role of d-dimer testing frequency as it relates to VTE and patient outcomes is unclear.

The majority of respondents utilized CRP in clinical care to either aid in steroid dose or duration or workup a secondary infection. A decrease in the CRP was thought to be the best marker of improvement by some of the providers surveyed. In a review of over 4,000 patients, only 3.6% had a secondary bacterial or fungal infection.[12] Over 71% of the entire cohort received broad spectrum antibiotics and 65% were admitted to the ICU. On average, a secondary bacterial or fungal infection was correlated with a maximum CRP of greater than 20 mg/dL. Interestingly, 95% of the respiratory coinfections occurred in intubated patients and only 6% had a positive bacterial culture prior to or on the same day of a positive SARS-CoV-2 PCR, suggesting a potential nosocomial source. Thus, while CRP use was not as frequent as d-dimer use, targeted use when a secondary infection is suspected may be useful. Whether this requires daily monitoring is less clear.

There is not compelling evidence in the literature regarding the use of CRP to guide corticosteroid therapy. The *CoDEX* clinical trial

Table 2. Physician utilizations of various COVID-19 inflammatory markers.*

	Method of utilization	Physician response (%)	Steroid dose/ duration (%)	Anticoagulation (%)	Secondary infection (%)
d-dimer	Change in management	83.1	0.0	93.8	6.3
	Trending inflammation	1.3			
	Not using	14.3			
	No response	1.3			
Ferritin	Change in management	46.8	62.0	6.5	31.5
	Trending inflammation	2.6			
	Not using	49.4			
	No response	1.3			
CRP**	Change in management	61.0	57.1	7.1	35.8
	Trending inflammation	3.9			
	Not using	33.8			
	No response	1.3			
LDH***	Change in management	39.0	50.0	13.3	36.7
	Trending inflammation	0.0			
	Not using	59.7			
	No response	1.3			

*Depicting the method of utilization for d-dimer, ferritin, CRP, and LDH as a percentage of the total number of physicians surveyed. Change in management was split further into steroid dosing/duration, dosing of anticoagulation, and workup of a secondary infection. This is a percent of the group who utilized the lab value for change in management only.
**CRP = c-reactive protein.
***LDH = lactate dehydrogenase.

Table 3. Obtaining inflammatory markers in "recovered" COVID-19 patients.*

Level of support	Obtaining markers		Response (%)
Mechanical ventilation	Yes	14	43.8
	No	18	56.3
	N/A	45	
Heated high flow nasal canula	Yes	30	56.6
	No	23	43.4
	N/A	24	
Nasal canula	Yes	30	39.0
	No	47	61.0
	N/A	0	

*"Recovered" is designated to patients with a prior positive SARS-CoV-2 Polymerase Chain Reaction assay who no longer require isolation. Selections under N/A represent that a provider does not manage patient requiring that level of support. The percent response does not include the N/A group.

evaluated ARDS dosed dexamethasone (20 mg for five days followed by 10 mg for five days) against routine care (no steroid).[13] The study was terminated early for ethical reasons after findings of RECOVERY were published. A metanalysis of seven trials did not show evidence that higher dose corticosteroid improved mortality over a lower dose in critically ill patients.[14] None of these studies, however, provided any evidence regarding guiding corticosteroid therapy by CRP as was reported to be done frequently by our surveyed physicians.

There was no consensus in how LDH or ferritin was utilized among the physicians surveyed in our study. Though ferritin level on admission is helpful in determining severity of disease, there is no evidence to suggest utility of serial monitoring to guide therapeutic decision making.[3,9] The split in responses may be a reflection of the lack of literature, suggesting its use as a general marker of inflammation.[9]

Similar to ferritin, the literature was lacking in regard to the role of LDH outside of prognostication on initial presentation. Most providers did not feel that measuring LDH was beneficial to patient care.

The institution's IPAC group designated patients who no longer require isolation as "recovering". At TUKHS, this "recovered" status is defined for immunocompetent patients as 10 days from a positive test result. Most physicians did not order inflammatory markers on "recovering" patients requiring supplemental oxygen via nasal cannula or even mechanical ventilation. A third survey question was presented considering heated high flow nasal cannula (HHFNC). The data were disregarded as institutional policy was changed two weeks after the survey had been distributed. Prior to distribution, HHNFC required ICU status. The change allowed floor patients meeting certain criteria to use HHFNC. Majority of providers checked inflammatory markers on these patients. This may reflect a level of comfort with the clinical status of the patient or some confusion regarding the differences in HHFNC and high flow nasal cannula, which was previously available for floor status patients. Most survey respondents valued the inflammatory markers in the first 10 days of hospitalization.

Based on the results of the survey and the current available evidence, it may be reasonable to implement three changes to the current standard of practice at our institution. It is practical to obtain ferritin and LDH on admission for prognostication purposes, but frequent monitoring is of unclear importance and does not have a significant effect on patient management. Second, discontinuation of d-dimer monitoring on patients requiring therapeutic anticoagulation prior to admission for an underlying condition such as atrial fibrillation, deep vein thrombosis, pulmonary embolism, mechanical heart valve, or left ventricular assist device. Finally, a limitation for daily orders for CRP and d-dimer to 10 days via the order set with an alternative selection to monitor less frequently could be considered. Inflammatory markers orders outside of these parameters would not be restricted but would require the provider to order the marker as a stand-alone test when it is felt to be necessary.

By eliminating both LDH and ferritin from the standardized order set, our hospital system could save over $15 per patient day. This represents $10,570 savings to our health system during an average week based upon a COVID-19 inpatient census of around 100 if admitting physicians do not extend LDH and ferritin outside of the order set.

A strength of this study was the collection of data from the first year of the pandemic including 2,369 patients at a large tertiary care center in the Midwest, in addition to physician feedback and financial analysis that were used to modify the existing algorithm for our healthcare system. This information was timely, when no available guidance for physicians regarding utility of these inflammatory markers in the management in COVID-19.

The primary limitations to this study were the relatively small sample size and response rate. Only 125 physicians were surveyed (focusing on physicians who cared for the majority of admitted COVID-19 patients) and of that group only 77 completed the survey. As a result, there was increased risk for selection bias from practitioners who cared for fewer COVID-19 patients overall. Two of the groups of surveyed physicians were also specialists in the fields of Infectious Diseases and Pulmonary and Critical Care medicine and may have been more aware of research in the area of COVID-19 related diagnostic and prognostic markers. Furthermore, this was a single institution which limited practice variability given a single electronic medical record, a single supervisory COVID-19 management taskforce, and single specialist group of Infectious Diseases and Pulmonary and Critical Care consultants. Surveying multiple institutions and limiting the surveys to providers immediately after completing a service block managing COVID-19 patients may limit some bias, as would have opening the survey to all physicians at the institution with admitting privileges. Additionally, correlating the survey data with true usage information would inform true use patterns better as they relate to therapeutic changes and patient outcomes. Opening the survey for a more prolonged period may have recruited more responses from the intended survey group (125 physicians) but was intended to be brief given the rapid changing climate of COVID-19 related admissions.

If the changes described above are implemented, additional data related to ICD-10 codes for secondary infections, total length of stay, ICU length of stay, and mortality before and after an order-set change intervention could be carried out to monitor for possible effects of those changes. A cost-savings analysis comparing the number of tests both directly and indirectly (e.g., computed tomography angiography, lower extremity ultrasound doppler, sputum culture, blood culture) related to this study before and after the proposed order set changes also could be considered.

In conclusion, physicians within our institution who primarily were managing patients with COVID-19 favored checking d-dimer and CRP daily for at least three to five days. Most physicians did not utilize ferritin or LDH routinely for inpatient management decisions. Therefore, as a diagnostic stewardship initiative, the institutional algorithm was changed after analyzing the ordering pattern through physician survey responses. Future studies could assess safety outcomes by comparing one-month mortality and length of hospital stay in the preintervention and postintervention groups.

REFERENCES

1   Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020; 55(3):105924. PMID: 32081636.

2   Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Inf Dis 2020; 20(5):533-534. PMID: 32087114.

3   Garibaldi BT, Fiksel J, Muschelli J, et al. Patient trajectories among persons hospitalized for COVID-19: A cohort study. Ann Intern Med 2021; 174(1):33-41. PMID: 32960645.

4   Aloisio E, Chibireva M, Serafini L, et al. A comprehensive appraisal of laboratory biochemistry tests as major predictors of COVID-19 severity. Arch Pathol Lab Med 2020; 144(12):1457-1464. PMID: 32649222.

5   Tjendra Y, Al Mana AF, Espejo AP, et al. Predicting disease severity and outcome in COVID-19 patients: A review of multiple biomarkers. Arch Pathol Lab Med 2020; 144(12):1465-1474. PMID: 32818235.

6   RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 - Preliminary report. N Engl J Med 2020; 384(8):693-704. PMID: 32678530.

7   Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18(5):1094-1099. PMID: 32220112.

8   RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2021;397(10285):1637-1645. PMID: 33933206.

9   Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. Int J Infect Dis 2020; 96:467-474. PMID: 32425643.

10   Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J Am Coll Cardiol 2020; 75(23):2950-2973. PMID: 32311448.

11   Nadkarni GN, Lala A, Bagiella E, et al. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. J Am Coll Cardiol 2020; 76(16):1815-1826. PMID: 32860872.

12   Nori P, Cowman K, Chen V, et al. Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge. Infect Control Hosp Epidemiol 2021; 42(1):84-88. PMID: 32703320.

13   Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. JAMA 2020; 324(13):1307-1316. PMID: 32876695.

14   WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA 2020; 324(13):1330-1341. PMID: 32876694.