Prognostic Value of Inflammatory Markers in Hospitalized COVID-19 Patients: A Retrospective Cohort Study

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Abstract

It is unclear whether D-dimer is a disease-specific marker for COVID-19 or part of the general inflammatory response alongside C-reactive protein (CRP) and other acute-phase reactants. We extracted data of patients hospitalized with COVID-19 for demographics, comorbidities, biochemical data, and outcomes. Using multivariable logistic regression, the value of D-dimer in predicting intensive care unit (ICU) admission or mortality was measured. Of 1175 patients, 263 were admitted to the ICU and 226 died. CRP predicted both ICU admission and mortality [Odds ratios (ORs) with 95% confidence interval 1.01 (1.01–1.01) and 1.00 (1.00–1.01), respectively] but D-dimer was not predictive of either outcome [ORs 1.02 (0.97–1.06) and 0.99 (0.93–1.06)]. This suggests D-dimer levels are not independently predictive of COVID-19 severity or mortality. Our results confirm findings from smaller cohorts and demonstrate the inflammatory characteristics of COVID in the Canadian context.

Résumé

On ne sait pas exactement si le D-dimère est un marqueur propre à la COVID-19 ou s'il fait partie de la réponse inflammatoire générale au même titre que la protéine C réactive et autres réactifs de phase aiguë. Nous avons extrait les données relatives aux caractéristiques démographiques, aux affections comorbides, aux analyses biochimiques et aux issues de patients hospitalisés en raison de la COVID-19. À l'aide d'une régression logistique multivariable, nous avons mesuré l'utilité du D-dimère dans la prédiction de l'admission à l'unité des soins intensifs (USI) ou de la mortalité. Sur 1175 patients, 263 ont été admis à l'USI et 226 sont décédés. La protéine C réactive a permis de prédire l'admission à l'USI (rapport de cotes [RC] = 1,01; intervalle de confiance [IC] à 95 % de 1,01 à 1,01) et la mortalité (RC = 1,00; IC à 95 % de 1,00 à 1,01), mais le D-dimère n'a pas permis de prédire l'une ou l'autre issue (RC = 1,02; IC à 95 % de 0,97 à 1,06 pour l'admission à l'USI et RC = 0,99; IC à 95 % de 0,93 à 1,06 pour la mortalité). D'après ces résultats, les taux de D-dimère ne sont pas des prédicteurs indépendants de la gravité de la COVID-19 ou de la mortalité. Nos résultats confirment les résultats de cohortes plus petites et démontrent les caractéristiques inflammatoires de la COVID-19 dans le contexte canadien.

Keywords: COVID-19, coronavirus, d-dimer, coagulation, inflammation

Introduction

COVID-19 infections have variable clinical severity, and outcomes, with a marked age-mortality gradient.[1] Consequently, risk factors that are associated with poor outcomes have been sought out for prognostication and therapeutic decision making. D-dimer has been found to be useful in prognostication[1] with up to 46% of COVID-19 patients having elevated levels. D-dimer has also been shown to predict mortality; in one study, COVID-19 non-survivors were found to have serum D-dimer levels more than three times greater than their surviving counterparts.[2]

However, D-dimer is a sensitive but non-specific biomarker that can be seen in many thrombotic and pro-inflammatory states, both of which are induced by COVID infection.[1,3] Therefore, differentiation is required between inflammatory and thrombotic contributors. Several models have also examined C-reactive protein (CRP) levels, a measure of inflammation,[4] in COVID-19 prognostication.[5] Research has shown that while D-dimer and CRP levels are both prognostic, it is not clear if they are collinear or portend separate risks.[4,6] Delineating whether D-dimer is more reflective of inflammation or coagulation would allow for more refined decision-making when caring for individuals with COVID-19. As such, this study assesses the prognostic value of different markers of inflammation and coagulation in Canadian patients hospitalized with COVID-19.

Methods

We analyzed a cohort of all hospitalized patients with a positive polymerase chain reaction (PCR) test for COVID-19 from four centers using the McMaster Multi-Regional Hospital Coronavirus Registry (COREG) between March 4, 2020 and June 24, 2021. Patients were included in the further analysis if data were available for them regarding all variables in question. Our study received ethics approval from the Hamilton Integrated Research Ethics Board (HiREB #12970-C) and Tri-Hospital Research Ethics Board (THREB #2020-0719).

The following variables were collected: age, sex, days since symptom onset, hemoglobin, white cell count, lymphocytes, neutrophils, platelets, CRP, D-dimer, INR, PTT, ferritin, and creatinine. Values used were those measured within 24 h of admission. Data concerning the following baseline comorbidities were extracted: coronary artery disease, chronic cardiac disease, ischemic stroke, hypertension, asthma and/or Chronic Obstructive Pulmonary Disease (COPD), diabetes, chronic kidney disease, liver disease, dementia, history of deep vein thrombosis (DVT) or a pulmonary embolism (PE), and the presence of two or more comorbidities. Deep vein thromboses, pulmonary emboli, and the need for supplemental oxygen during admission were collected. Primary outcomes were intensive care unit (ICU) admission and mortality.

Data were described using mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Patients were stratified by ICU admission or in-hospital mortality and outcomes by level of D-dimer elevation. For each outcome, multivariable logistic regression using CRP, D-dimer, INR, platelets, and age was performed.

An exploratory analysis was performed to determine if co-infection or complications of stay affected CRP levels. Univariate analysis between CRP and the following infections was performed: urinary tract infections (UTIs), abscesses, bacteremia, bacterial pneumonia, cellulitis, and meningitis/encephalitis. Where an association with $p < 0.05$ was found, a separate regression was performed including the infections to determine the infection's effect on inflammatory markers.

Results

Data for 1175 individuals were available. 53.8% of the cohort was male and the median age was 70 years; 263 (22.4%) were admitted to ICU and 226 (19.2%) died. The median time since symptom onset for all patients was 4 days. Those who were either admitted to ICU or died had higher D-dimer, CRP, white cell count, and creatinine. Those who were admitted to ICU were younger and more often male. Diabetes mellitus, liver disease, and dementia were more frequent in those who were admitted to ICU. Those who died had higher rates of all comorbidities except liver disease (Table 1).

Of those admitted to ICU (N = 263), 125 were admitted directly to ICU, and 138 were initially admitted to the ward and later transferred to ICU. Patients initially admitted to the ward (N = 1050) had a mortality rate of 17.5% and patients admitted directly to ICU (N = 125) had a mortality rate of 33.6%.

Table 1. Univariate regression comparing ICU admission and mortality outcomes in COVID-19 patients

	Total (N = 1175)	ICU			Mortality		
		No (N = 912)	Yes (N = 263)	P value	No (N = 949)	Yes (N = 226)	P value
Age *(years)*	70.0 (55.0–83.0)	72.0 (54.0–84.0)	68.0 (57.0–77.0)	0.011	67.0 (51.0–79.0)	82.0 (74.0–88.0)	<0.001
Male	632 (53.8%)	464 (50.9%)	168 (63.9%)	<0.001	512 (54.0%)	120 (53.1%)	0.82
Days since symptom onset	4.0 (1.0–8.0)	4.0 (1.0–8.0)	5.0 (1.0–9.0)	0.06	4.0 (1.0–8.0)	2.0 (0.0–7.0)	<0.001
White blood cells *(10^9 cells/L)*	6.6 (4.8–9.1)	6.4 (4.6–8.7)	7.1 (5.6–10.3)	<0.001	6.4 (4.7–8.5)	7.4 (5.3–10.8)	<0.001
Lymphocytes *(10^9 cells/L)*	0.9 (0.7–1.4)	1.0 (0.7–1.4)	0.9 (0.6–1.2)	<0.001	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.003
Neutrophils *(10^9 cells/L)*	4.6 (3.1–6.9)	4.5 (3.0–6.5)	5.4 (4.0–8.2)	<0.001	4.5 (3.1–6.6)	5.4 (3.6–8.5)	<0.001
Platelets *(cells/μL)*	203.0 (155.5–261.5)	206.0 (158.0–265.0)	194.0 (150.0–256.0)	0.14	205.0 (161.0–263.5)	198.0 (136.0–260.0)	0.008
D-dimer *(μg/mL)*	1.2 (0.6–2.8)	1.0 (0.5–2.2)	1.5 (0.8–3.9)	0.001	1.0 (0.5–2.3)	1.9 (1.1–4.0)	<0.001
CRP *(mg/L)*	69.4 (24.5–150.0)	47.2 (15.6–121.9)	123.0 (63.7–185.6)	<0.001	61.1 (17.7–140.6)	107.4 (56.9–167.5)	<0.001
INR *(seconds)*	1.1 (1.0–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.007	1.1 (1.0–1.2)	1.2 (1.0–1.4)	<0.001
PTT *(seconds)*	32.0 (29.0–36.0)	32.0 (29.0–35.0)	33.0 (29.0–38.0)	0.18	33.0 (29.0–36.0)	32.0 (27.0–36.0)	0.28
Ferritin *(μg/L)*	489.5 (158.0–969.0)	371.0 (114.0–714.0)	756.8 (343.5–1339.5)	<0.001	473.0 (150.0–942.3)	623.6 (325.0–1044.1)	0.22
Creatinine *(μmol/L)*	83.0 (63.0–112.0)	80.0 (61.0–108.0)	88.1 (67.0–132.0)	0.001	78.0 (60.0–104.0)	104.0 (78.0–141.0)	<0.001
Developed DVT/PE	18 (1.56%)	5 (0.56%)	13 (4.98%)	<0.001	10 (1.08%)	8 (3.57%)	0.013
Required oxygen therapy	689 (58.64%)	437 (47.92%)	252 (95.82%)	<0.001	490 (51.63%)	199 (88.05%)	<0.001
Comorbidities							
Ischemic stroke	110 (9.36%)	93 (10.20%)	17 (6.46%)	0.07	78 (8.22%)	32 (14.16%)	0.006
Chronic cardiac disease	189 (16.09%)	143 (15.68%)	46 (17.49%)	0.48	129 (13.59%)	60 (26.55%)	<0.001
Hypertension	644 (54.81%)	488 (53.51%)	156 (59.32%)	0.1	489 (51.53%)	155 (68.58%)	<0.001
Asthma and/or COPD	284 (24.19%)	223 (24.48%)	61 (23.19%)	0.67	210 (22.13%)	74 (32.89%)	<0.001
Diabetes (Type 1 and Type 2)	394 (33.53%)	286 (31.36%)	208 (41.06%)	0.003	89 (9.38%)	48 (21.24%)	0.038
Chronic kidney disease	137 (11.66%)	101 (11.07%)	36 (13.69%)	0.24	89 (9.38%)	48 (21.24%)	<0.001
Liver disease	35 (2.98%)	20 (2.19%)	15 (5.70%)	0.003	24 (2.53%)	11 (4.87%)	0.06
Dementia	159 (13.53%)	148 (16.23%)	11 (4.18%)	<0.001	105 (11.06%)	54 (23.89%)	<0.001
Prior history of DVT/PE	64 (5.45%)	51 (5.59%)	13 (4.94%)	0.68	41 (4.32%)	23 (10.18%)	<0.001
One or more comorbidities	868 (73.87%)	699 (73.36%)	199 (75.67%)	0.45	661 (6965%)	207 (91.59%)	<0.001
Two or more comorbidities	636 (54.13%)	484 (53.07%)	152 (57.79%)	0.18	462 (48.68%)	174 (76.99%)	<0.001

C-Reactive Protein (CRP), International Normalized Ratio (INR), Partial Thromboplastin Time (PTT), Chronic Obstructive Pulmonary Disease (COPD), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE).

Values are expressed as median and IQR.

Table 2. Multivariate regression comparing ICU admission and mortality outcomes in COVID-19 patients

	ICU (N = 192)		Mortality (N = 192)	
Effect	**Point estimate**	**95% Confidence intervals**	**Point estimate**	**95% Confidence intervals**
D-dimer *(μg/mL)*	1.02	0.97–1.06	0.99	0.93–1.06
INR	0.98	0.85–1.12	1.05	0.90–1.23
CRP *(mg/L)*	1.01	1.01–1.01	1.00	1.00–1.01
Platelets *(10^9 cells/L)*	1.00	1.00–1.00	1.00	1.00–1.01
Age *(years)*	0.99	0.98–1.01	1.10	1.06–1.14

C-Reactive Protein (CRP), International Normalized Ratio (INR).

Complete data for inclusion in the multivariable analysis were available for 192 individuals. Increased platelets and CRP were found to predict both ICU admission and mortality. Increasing age was also predictive of mortality. D-dimer and INR were not predictive of either outcome (Table 2).

Results of the sensitivity analysis demonstrated a significant association between CRP levels and bacteremia (n = 77) as well as meningitis/encephalitis (n = 5). Meningitis/encephalitis was excluded from multivariable analysis due to low event number causing model instability. For ICU admission, CRP remained a significant prognosticator alongside bacteremia [Odds ratios (ORs) with 95% confidence interval 1.01 (1.00–1.01) and 5.72 (1.44–22.63), respectively]. For mortality, the only significant prognosticator for mortality was age [OR 1.10 (1.06–1.14)] meanwhile CRP was no longer significant [OR 1.00 (1.00–1.01)]. For both ICU admission and mortality, D-dimer remained non-significant [OR 1.02 (0.98–1.06) and 0.99 (0.93–1.06), respectively].

Discussion

In our cohort of Canadian patients admitted to the hospital with COVID-19, an elevated D-dimer was not an independent risk factor for ICU admission and mortality. This observation is in line with a systematic review by Gungor et al.,[6] which showed that among all recent studies on the role of D-dimer in COVID-19 patients, only four examined D-dimer as a prognostic marker in both univariate and multivariate analyses and none reached statistical significance in their multivariate analysis. CRP, however, was a good predictor for adverse events in both univariate and multivariate analyses. Our findings also align with previous work[4,6] showing that inflammation is a driver of COVID-19 disease progression. Prior studies also showed that CRP can be used to track the recovery of COVID-19 patients[4] and predict the need for mechanical ventilation.[7]

In our exploratory analysis, CRP was not a significant prognosticator for mortality when bacteremia was included as a covariate. These findings should be interpreted with caution as acute phase reactants were measured only at the hospital admission, whereas bacteremia may have occurred at any point during a patient's stay at the hospital. Further analysis is required to better delineate the predictive value of CRP when accounting for complications of COVID-19 infection. However, our observation that D-dimer lacked prognostic value was reaffirmed.

Our study had several strengths. Our sample size of 1175 individuals compares favorably to other retrospective cohort studies of COVID-19 patients. Using the COREG database, we had access to a wide range of laboratory values, comorbidity data, and medical complications allowing for a methodologically robust analysis that included all relevant covariates. To our knowledge, this is the first study that examined the role of D-dimer and CRP as prognostic markers for COVID-19 infection in an exclusively Canadian cohort. Further, our work considered several causes of CRP elevation and thus accounted for many common complications of COVID-19 infection.

Our findings also have limitations that merit consideration. There was variability between laboratory tests that were ordered for inpatients, with potential selection bias depending on the severity of a patient's disease. Data on some important comorbidities were not available (e.g., peptic ulcer disease) which limited our ability to employ validated comorbidity scores, such as the Charlson Comorbidity Index.[8]

Our results suggest that D-dimer levels do not independently predict COVID-19 disease progression or mortality. This observation is largely consistent with previous reports but is now confirmed in a Canadian cohort. Future research should be directed towards further exploring prognostic markers of COVID-19 patients to improve risk stratification and treatment.

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Conflicts of Interest

None of the other authors have any relevant conflicts of interest.

Author Contributions

All authors contributed to the manuscript at least in one of the five following categories: conception and design, procurement of data, analysis of data, drafting of the original manuscript, and critical review of the original manuscript.

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