Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Sex differences in the prognostic value of troponin and D-dimer in COVID-19 illness

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ABSTRACT

Background: Male sex, elevated troponin levels, and elevated D-dimer levels are associated with more complicated COVID-19 illness and greater mortality; however, while there are known sex differences in the prognostic value of troponin and D-dimer in other disease states, it is unknown whether they exist in the setting of COVID-19.

Objective: We assessed whether sex modified the relationship between troponin, D-dimer, and severe COVID-19 illness (defined as mechanical ventilation, ICU admission or transfer, discharge to hospice, or death).

Methods: We conducted a retrospective cohort study of patients hospitalized with COVID-19 at a large, academic health system. We used multivariable regression to assess associations between sex, troponin, D-dimer, and severe COVID-19 illness, adjusting for demographic, clinical, and laboratory covariates. To test whether sex modified the relationship between severe COVID-19 illness and troponin or D-dimer, models with interaction terms were utilized.

Results: Among 4,574 patients hospitalized with COVID-19, male sex was associated with higher levels of troponin and greater odds of severe COVID-19 illness, but lower levels of initial D-dimer when compared with female sex. While sex did not modify the relationship between troponin level and severe COVID-19 illness, peak D-dimer level was more strongly associated with severe COVID-19 illness in male patients compared to female patients (males: OR=2.91, 95%CI=2.63-2.34, $p<0.001$; females: OR=2.31, 95%CI=2.04-2.63, $p<0.001$; p-interaction=0.005).

Conclusion: Sex did not modify the association between troponin level and severe COVID-19 illness, but did modify the association between peak D-dimer and severe COVID-19 illness, suggesting greater prognostic value for D-dimer in males with COVID-19.

Introduction

Myocardial injury is associated with worse prognosis in patients with COVID-19.[1-7] Numerous mechanisms for myocardial injury in COVID-19 have been proposed, including microvascular thrombosis, increased risk of coronary plaque destabilization, myocarditis, endothelial dysfunction, injury due to systemic inflammatory response, and supply-demand mismatch.[8]

Male sex is also associated with more complicated COVID-19 disease course and greater mortality.[1,3,9,10] However, the relationship between sex and myocardial injury in patients with COVID-19 remains in question, with some studies reporting higher troponin levels among men[11] and others finding no difference.[9] Prior to the COVID-19 pandemic, sex differences in troponin were described in healthy patients and in those with ischemic heart disease and acute coronary syndromes.[12] These studies found lower troponin levels

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among women, and poorer outcomes among women compared to men at the same degree of troponin elevation.

Sex differences in venous thrombosis could also play a role. Venous thrombosis is a prominent feature of COVID-19 and higher D-dimer levels, a surrogate marker for thrombosis, have been associated with poorer prognosis.[1,6,13] Prior to the COVID-19 pandemic, higher D-dimer levels have been reported in females in the setting of both chronic disease [14] and critical illness.[15] Unlike cardiac troponin, which has a lower sensitivity in *women* with coronary artery disease,[12] D-dimer can have a lower sensitivity in *men* with thrombotic disease.[16]

It is unknown whether these previously described sex differences in the prognostic value of troponin and D-dimer also exist in the setting of COVID-19. Therefore, we studied a large, diverse population of patients hospitalized with COVID-19 in New York City to assess whether sex modifies the relationship between troponin, D-dimer, and COVID-19 outcomes. We hypothesized that, similar to some other disease states, the association between these two biomarkers and COVID-19 outcome would be different for male patients as compared to female patients.

Methods

We conducted a retrospective cohort study of all patients hospitalized at a large, multi-hospital, urban, academic health system in New York City between March 1, 2020 and December 7, 2020 who had a positive SARS-CoV-2-PCR and available cardiac troponin I or D-dimer levels. This study was approved by the NYU Institutional Review Board, which granted a waiver of informed consent.

Our primary outcome of interest was severe COVID-19 illness, which was defined as composite outcome of mechanical ventilation, ICU admission or transfer, discharge to hospice, or death, as previously described.[13] Using the electronic health record, we obtained the following data: age, sex, patient-reported race and ethnicity, tobacco use, and body mass index (BMI), using a de-identified data extract. We also extracted the following medical history using documented diagnostic codes or encounter diagnoses: hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease (COPD), heart failure, and chronic kidney disease. We recorded initial and peak troponin I levels, initial and peak D-dimer levels initial white blood cell count, absolute lymphocyte count, ferritin, C-reactive protein (CRP), pro-calcitonin, creatinine, and aspartate aminotransferase (AST). All NYU hospitals utilized the same troponin I assay (Abbott, Abbott Park, IL, USA), with upper limit of normal of 0.04 ng/mL. Additionally, all hospitals measured D-dimer with the Hemosil D-dimer HS 500 on an automated coagulation analyzer (ACL TOP, Instrumentation Laboratory), with an upper limit of normal of 230 ng/mL.

We used descriptive statistics to characterize differences in demographics, medical history, laboratory values, and outcomes by sex. Categorical variables were compared using chi-squared or Fisher's exact test, as appropriate, and continuous variables were compared using two-sample t or Mann-Whitney U test based on normality of data. Unadjusted rates of severe COVID-19 illness according to sex and degree of troponin and D-dimer elevation were compared using the two-proportion Z-test. Linear regression models were used to assess the association of troponin and D-dimer levels with sex, and were log transformed to meet the normality assumption. Multivariable logistic regression models were used to assess association of severe COVID-19 infection with sex, as well as initial and peak troponin and D-dimer levels. To assess whether sex modified the relationship between troponin (initial and peak) or D-dimer (initial and peak) and severe COVID-19 infection, four additional logistic regression models with interaction terms were utilized. Models were adjusted for demographics, medical history, and the other laboratory values as listed above. These variables were chosen based on prior literature suggesting importance in COVID-19 illness severity.[13] Model performance was assessed using Area Under the Curve (AUC) and the Hosmer and Lemeshow goodness-of-fit (GOF) statistics.[17] All analyses were conducted using R 3.5.2 (Vienna, Austria). We used a two-sided p-value of <0.05 as threshold for statistical significance.

Results

A total of 5,063 patients who tested positive for COVID-19 were hospitalized at 5 NYU Langone Health hospitals between March 1 and December 7, 2020. After exclusion of patients without available serum troponin or D-dimer levels (n=489), our final sample included 4,574 patients (58.5% male, 55.8% $\geq$63 years). Women were less likely to have chronic kidney disease (22.4% vs 25.5%, p=0.018) or a smoking history (21.1% vs 29.4%, $p<0.001$, Table 1) and had lower levels of CRP, ferritin, and pro-calcitonin.

Initial troponin levels were similar by sex (p=0.436), but peak troponin was slightly higher in males (median 0.08 ng/mL, interquartile range [IQR] 0.00-0.11 vs 0.06 [0.01-0.10], p=0.001, Table 2). After multivariable adjustment using linear regression, this association remained, with male sex being associated with a 15% higher peak troponin level (beta=0.14, 95% CI=0.02-0.27, p=0.023). In contrast, female patients had higher initial D-dimer (458 [255-915] vs 404 [245-805] ng/mL, p=0.008), but lower peak D-dimer (736 [357-2,391] vs 839 [358-3,539] ng/mL, $p<0.001$). After multivariable adjustment, this association was no longer seen for peak D-dimer, but persisted for initial D-dimer, with males having 13% lower initial D-dimer levels as compared to females (beta=-0.14, 95% CI=-0.22 to -0.06, p=0.001).

The primary composite outcome of severe COVID-19 occurred in 1,559 (34.1%) patients (Table 2). Fewer than 5% (4.9%) of the patients in our cohort met the outcome based on ICU admission alone (without mechanical ventilation or mortality). Additionally, over 50% experienced more than 1 event (16.7% had ICU and mechanical ventilation, 11.7% had ICU and mortality, 12.3% had mechanical ventilation and mortality), and 10.3% had all of these three events: ICU, mechanical ventilation and mortality. Males were more likely to have severe COVID-19 (38.8% vs 32.4%, $p<0.001$), driven by higher rates of ICU care (27.7% vs 18.6%, $p<0.001$) and mechanical ventilation (23.1% vs 15.5%, $p<0.001$). After multivariable adjustment with logistic regression including initial laboratory values, males had higher odds of severe COVID-19 (OR=1.33, 95% CI=1.11-1.60, p=0.002), but this association was diminished after additional adjustment for peak troponin and D-dimer (OR=1.18, 95% CI = 0.95-1.47, p=0.134).

In adjusted multivariable logistic regression models, initial and peak troponin levels were associated with higher odds of severe COVID-19 (initial: OR=1.16 per ng/mL, 95% CI=1.08-1.25; and peak: OR=1.66 per ng/mL, 95% CI=1.56-1.78, $p<0.001$). These associations were not modified by sex (Fig. 1). Both initial and peak D-dimer levels were also associated with higher odds of severe COVID-19 illness (initial: OR=1.34 per 1000 ng/L, 95% CI=1.23-1.45, $p<0.001$; and peak: OR=2.67 per 1000 ng/mL, 95% CI=2.46-2.90, $p<0.001$). While sex did not modify the association between initial D-dimer level and severe COVID-19 illness, peak D-dimer level was more strongly associated with severe COVID-19 illness in males than females (male: OR=2.91, 95% CI=2.63-3.24 vs female: OR=2.31, 95% CI=2.04-2.63, p-interaction=0.005, Fig. 1). While all logistic regression models suggested good discrimination and calibration properties with AUCs $>$ 0.74 and non-significant Hosmer and Lemeshow GOF statistics, the model with peak D-dimer had the highest AUC, 0.86.

Discussion

In this study of 4,574 hospitalized patients with COVID-19, higher levels of troponin and D-dimer were associated with greater incidence of severe COVID-19 illness. This association was not modified

Table 1
Baseline characteristics.

Characteristic		Female, *N = 1898*	Male, *N = 2676*	p-value
Age *N (%)*	0-11	7 (0.4)	10 (0.4)	<0.001
	12-22	44 (2.3)	22 (0.8)	
	23-32	110 (5.8)	89 (3.3)	
	33-42	133 (7.0)	220 (8.2)	
	43-52	168 (8.9)	357 (13.4)	
	53-62	292 (15.4)	557 (20.9)	
	63-72	387 (20.5)	667 (25.0)	
	73-82	382 (20.2)	430 (16.1)	
	83+	367 (19.4)	318 (11.9)	
Ethnicity, N (%)				
Hispanic/Latino		500 (26.3)	763 (28.5)	0.095
Not of Hispanic/Latino Origin		1290 (68.0)	1738 (64.9)	
Unknown		108 (5.7)	175 (6.5)	
Race, N (%)				
African American (Black)		347 (18.3)	342 (12.8)	< 0.001
Asian		137 (7.2)	194 (7.2)	
White		847 (44.6)	1182 (44.2)	
Multiple		38 (2.0)	48 (1.8)	
Other		451 (23.8)	767 (28.7)	
Unknown		78 (4.1)	143 (5.3)	
Insurance, *N (%)*				
Medicaid		397 (20.9)	531 (19.8)	<0.001
Medicare		1029 (54.2)	1227 (45.9)	
Other		82 (4.3)	201 (7.5)	
Private		390 (20.5)	717 (26.8)	
Medical History, *N (%)*				
Hypertension		1156 (60.9)	1593 (59.5)	0.365
Diabetes		724 (38.1)	1051 (39.3)	0.458
COPD		180 (9.5)	211 (7.9)	0.064
Heart Failure		285 (15.0)	388 (14.5)	0.657
CKD		426 (22.4)	683 (25.5)	0.018
Hyperlipidemia		963 (50.7)	1345 (50.3)	0.774
Body mass index (kg/m$^{2)}$		28.29 [23.84, 33.28]	27.84 [24.60, 32.11]	0.260
Tobacco Use, *N (%)*				
Current		51 (2.8)	113 (4.4)	<0.001
Former		335 (18.3)	643 (25.0)	
Never		1226 (66.8)	1350 (52.6)	
Unknown		222 (12.1)	462 (18.0)	
Initial Laboratory Values, *median, [IQR]*				
Absolute lymphocyte count, 10^3/uL		1.00 [0.70, 1.50]	0.90 [0.60, 1.30]	<0.001
C-reactive protein, mg/L		75.10 [25.00, 142.80]	109.78 [50.11, 174.93]	<0.001
Ferritin, ng/mL		365.25 [141.00, 739.75]	861.20 [391.98, 1627.10]	<0.001
Procalcitonin, ng/mL		0.11 [0.05, 0.32]	0.18 [0.07, 0.49]	<0.001
Creatinine, mg/dL		0.87 [0.70, 1.22]	1.10 [0.90, 1.57]	<0.001
Aspartate aminotransferase, units/L		75.10 [25.00, 142.80]	109.78 [50.11, 174.93]	<0.001

COPD = Chronic Obstructive Pulmonary Disease, CKD = Chronic Kidney Disease, SD = standard deviation, IQR = interquartile range

by sex for cardiac troponin, but was modified by sex for peak D-dimer, with each unit increase in peak D-dimer associated with higher odds of severe illness among male patients, suggesting a greater prognostic value of D-dimer among males than females with COVID-19 infection.

Our results are consistent with previous findings that myocardial injury and D-dimer are associated with poorer prognosis in COVID-19 [7,13] and that male sex alone is also associated with a more complicated COVID-19 disease course.[9] However, this is the first study to our knowledge to show that sex modifies the relationship between D-dimer and outcomes of COVID-19 illness. Additionally, we found that sex did not modify the relationship between cardiac troponin and severe COVID-19 outcomes.

Multiple explanations for sex differences in COVID-19 outcomes have been proposed, such as a protective effect of estrogen, sex-specific differences in immune response such as differences in cytokine levels or T cell function, sex differences in endothelial function, and increased expression of angiotensin-converting enzyme 2 (ACE2, the functional receptor for SARS-CoV-2) in men, but none of these hypotheses have been proven to date.[18]

In chronic disease states such as diabetes, heart failure, and hypertension, female patients typically have higher D-dimer levels.[14] In this study of patients with COVID-19, we found similar sex differences for initial D-dimer levels, but in contrast, higher peak D-dimer levels in males compared to females. Furthermore, the same increment in D-dimer was associated with higher odds of severe illness among males after adjustment for other risk factors, indicating that D-dimer has greater prognostic value in males with COVID-19. Thrombosis is a prominent feature of COVID-19.[19] Sex differences in immune response,[18] hormones, platelet function, and vessel wall biology all have the potential to affect thrombus formation,[20] and these processes may be altered in COVID-19. Our findings highlight the need for further investigation.

In acute coronary syndrome, stable ischemic heart disease, myocarditis and even in healthy individuals, lower levels of troponin in females have been described, such that sex-specific thresholds for high sensitivity troponin assays are often recommended.[14] However, in patients with COVID-19, we found a similar prognostic value of troponin in both sexes, suggesting a different mechanism of cardiac injury.

Table 2
Sex differences in troponin, d-dimer, and primary outcomes.

	Female	Male	p-value
Troponin	*N = 1708*	*N = 2596*	
First troponin, ng/mL, median [IQR]	0.04 [0.01, 0.10]	0.04 [0.01, 0.10]	0.436
Adjusted** estimate of log(first troponin), beta (95% CI)	–	0.02 [-0.07, 0.11]	0.717
Peak troponin, ng/mL, median [IQR]	0.06 [0.01, 0.10]	0.08 [0.01, 0.11]	0.001
Adjusted** estimate of log(peak troponin), beta (95% CI)	–	0.14 [0.02, 0.27]	0.023
D-Dimer	*N = 1766*	*N = 2521*	
First D-dimer, ng/mL, median [IQR]	458.00 [255.00, 915.00]	404.00 [245.00, 805.00]	0.008
Adjusted** estimate of log(first D-dimer), beta (95% CI)	–	-0.14 [-0.22, -0.06]	0.001
Peak D-dimer, ng/mL, median [IQR]	736n.00 [357.00, 2391.25]	839.00 [358.00, 3539.00]	<0.001
Adjusted** estimate of log(peak D-dimer), beta (95% CI)	–	0.02 [-0.08, 0.12]	0.731
Outcomes, *N (%)*	*N = 1898*	*N = 2676*	
Severe COVID-19 Illness	553 (32.4)	1006 (38.8)	< 0.001
ICU Admission	318 (18.6)	720 (27.7)	< 0.001
Invasive Mechanical Ventilation	264 (15.5)	600 (23.1)	< 0.001
Death or Discharge to Hospice	379 (22.2)	648 (25.0)	0.040
Adjusted ** odds for severe COVID-19 infection, Male vs. Female, OR (95% CI)	–	1.33 (1.11-1.60)	0.002
Adjusted*** odds for severe COVID-19 infection, Male vs. Female, OR (95% CI)	–	1.18 (0.95-1.47)	0.134

*Abnormal troponin I defined as ≥ 0.04 ng/mL and abnormal D-dimer defined as >=230 ng/mL, based on local laboratory upper reference limit.
**Adjusted for age, race, ethnicity, BMI, smoking history, insurance, co-morbidities, and other initial laboratory values (as listed in Table 1), Area Under the Curve (AUC) for the model = 0.746.
***Adjusted for the above, peak troponin, and peak D-dimer, AUC = 0.873.

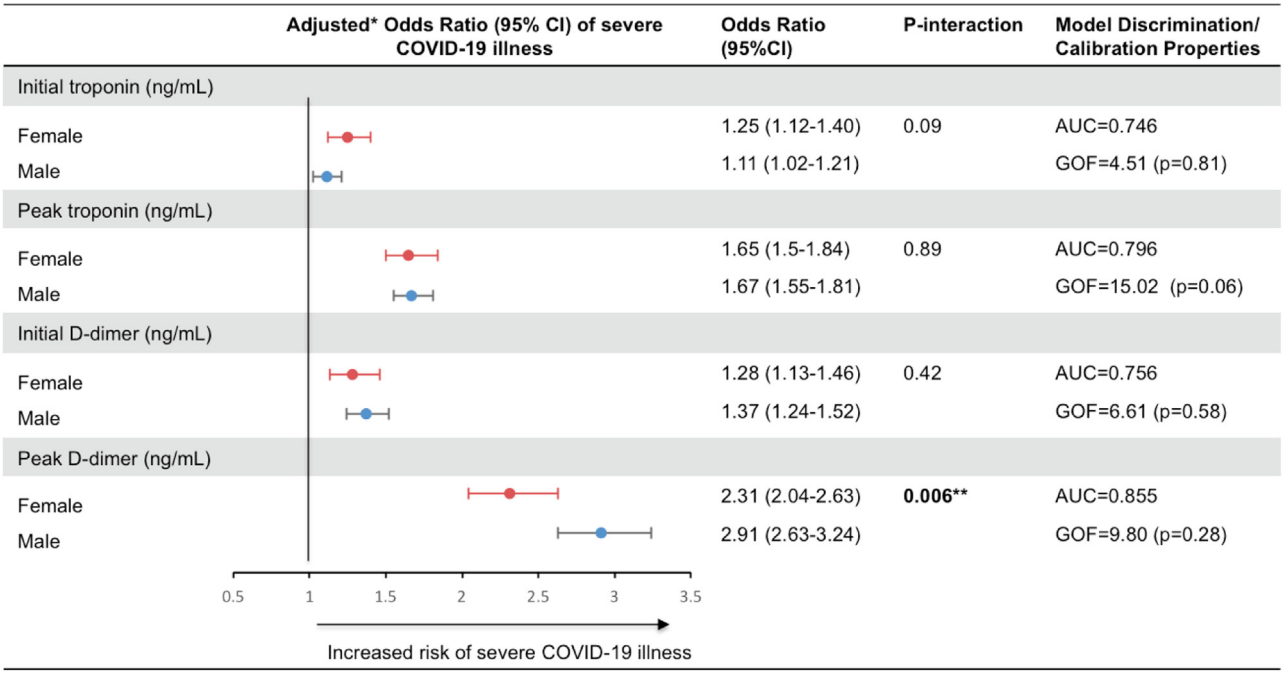

Fig. 1. Subgroup Analysis. Adjusted Odds of Severe COVID-19 Illness by Troponin and D-dimer levels, Stratified by Sex * Adjusted for age, race, ethnicity, BMI, insurance, smoking history, medical history, and other initial laboratory values (as listed in Table 1); overall cohort estimate includes sex in the multivariable model. ** p< 0.01 CI = Confidence Interval; AUC = Area Under the Curve; GOF = Goodness-of-fit.

Our single-center study was a retrospective analysis and therefore limited in ability to draw causal conclusions. Our data set did not include, illness severity on admission, symptoms, cause of death, ECGs, or echocardiogram results. Additionally, patients with available cardiac troponin and D-dimer measurements may have been inherently different from other patients without cardiac troponin and D-dimer measurements. Due to the de-identified nature of our data set, we did not have access to timing of outcome, and therefore could not conduct survival analysis. It was not possible for us to distinguish between different causes of troponin elevation, such as pulmonary embolism vs myocardial infarction or myocarditis.

Our findings highlight the importance of sex as a critical biological factor for developing severe COVID-19 illness. Specifically, our results underscore the valuable role for D-dimer in understanding this association, both as a prognostic marker, and as a key area for future research. Compared to females, males had lower initial D-dimer, greater peak D-dimer, and each unit rise in D-dimer was associated with greater odds of severe illness. These findings indicate that providers caring for patients with COVID-19 should not be reassured by a lower initial D-dimer, especially in a male patient. From an investigative perspective, it is critical that researches explicitly examine the role of sex when studying inflammation and thrombosis, both in

COVID-19 and also when studying other similar infectious disease processes.

Disclosure statement

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Conclusions

Unlike in the setting of ischemic heart disease, sex did not modify the relationship between elevated troponin and severe COVID-19 illness, perhaps related to differing mechanisms of myocardial injury. However, sex did modify the relationship between D-dimer and severe COVID-19, such that D-dimer had greater prognostic value in male patients. Future studies focused on mechanisms for thrombosis in COVID-19 should incorporate sex as an important biological variable.

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