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Joanna Bove

Robert Kim

Shelley Sanders

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Are elevated inflammatory markers and acute phase reactants associated with more severe disease in COVID 19 patients?

Joanna Bove, MD, MPH, Robert Kim, MD, Shelley Sanders, MD
Providence St. Vincent, Internal Medicine Residency, Portland, Oregon



Introduction

Inflammatory markers and acute phase reactants (from here referred to as “markers”) are associated with COVID-19 infection and may be able to predict disease severity.^{1,2} We collected markers including d-dimer (ug/mL), ferritin (ng/mL), CRP (mg/dL), and creatinine kinase (CK) (IU/L) on admission and periodically throughout the hospital stay for 50 patients admitted with COVID-19 infection. We hypothesized that higher levels of markers at admission and during hospitalization are associated increased severity of disease, such as ICU admission and placement on mechanical ventilation.

Methods

From March to May 2020, we identified 50 patients admitted to Providence St. Vincent Medical Center with PCR-confirmed COVID-19 infection. Demographic and laboratory data were obtained through chart review. Statistical analysis including linear regression, t-tests, and chi2 tests were performed to look at the association between markers and severe outcomes including ICU admission, mechanical ventilation, and inpatient mortality. Regression models were adjusted for patients’ age, gender, DM2 status, reported onset of symptoms, and whether the patient was hypoxic at admission. All the statistical analyses were carried out by STATA software (Version 16.1; STATA Corporation, College Station, TX, USA).

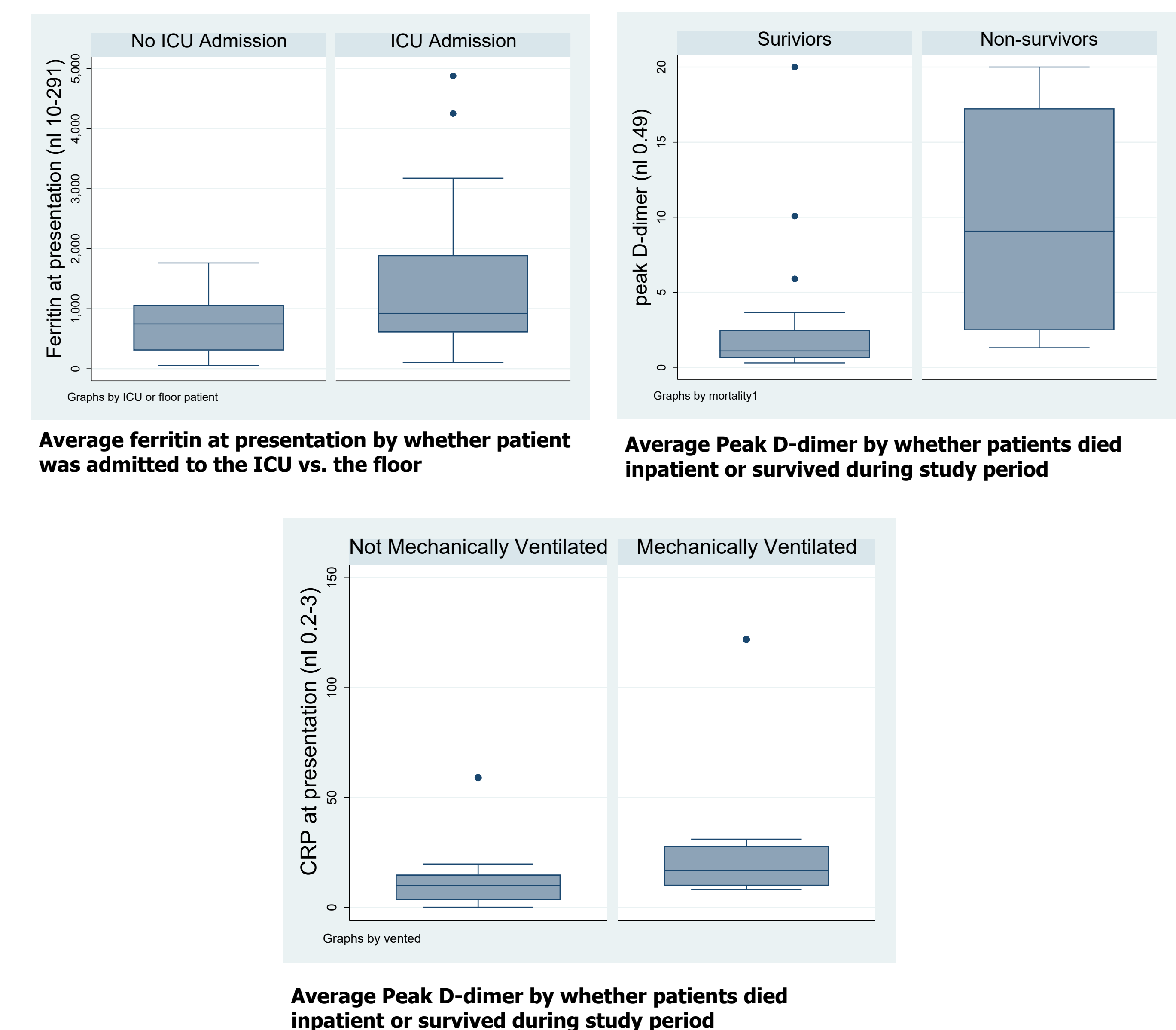
Results

There were 50 patients admitted for COVID-19 infection in March-May 2020. The average age was 60 yrs, and 46% (23) were female. Average reported duration of symptoms at admission was 7.9 days. 69% (33) of patients were hypoxic at admission, with SpO2 of <90% or requiring supplemental oxygen. 36% (n=18) of patients were admitted to the ICU during this time period. 28% (14) of patients were placed on mechanical ventilation, and 12% (6) died during their hospitalization (Table 1).

- The difference in mean admission markers between patients that were and were not hypoxic at admission were not statistically different.
- Patients who were admitted to the ICU had significantly higher ferritin levels at admission (ferritin difference 864.7, p=0.04); they also had significantly elevated peak CRP, ferritin, and CK, in comparison to patients admitted to the floor (CRP difference 13.6, p=0.01; Ferritin difference 1071.7; p=0.01, CK difference 561, p=0.03).
- Patients who had to be placed on mechanical ventilation had significantly higher CRP and ferritin levels at admission (CRP difference 21.5, p=0.04; ferritin difference 958.7, p=0.03); patients on mechanical ventilation also had increased peak levels of all markers (CRP difference 13.6, p=0.01, ferritin difference 1071.7, p=0.01; d-dimer difference 5.1, p=0.05; CK difference 626.3, p=0.02).
- Patients who died while in patient had higher d-dimer levels at admission (d-dimer difference 7.4, p=0.001); there was a trend in significance in the difference between peak CRP and ferritin levels among patients who died while inpatient.

Table 1: Descriptive statistics

Mean age (yrs)	60.26
Average reported duration of symptoms prior to presentation(days)	7.9 days
Average BMI	30.6
% hypoxic at admission (n)	68.8% (33)
% with DM2 (n)	27% (13)
% female (n)	46% (23)
% admitted to ICU (n)	36% (18)
% received mechanical ventilation (n)	26% (14)



Discussion

So while clinical features such as hypoxia are often indicators for increased surveillance (ICU admission) and mechanical intubation, elevated markers such as CRP, ferritin, d-dimer and CK are also associated with ICU admission and mechanical ventilation. Elevation in inflammatory markers such as CRP and ferritin have been demonstrated among severe cases of COVID-19 previously (Zeng, 2020). Surprisingly, different levels of inflammatory markers were not different among those presenting with and without hypoxia. Thus, inflammatory markers could be early warning signs for whether a COVID 19+ patient should be admitted, monitored at home, or triaged further. Similar to other studies, we found increasing levels of d-dimer was associated with mortality in COVID 19 patients.³

Limitations to this study include small sample size, differences in practices of collecting laboratory samples over time (more samples were collected in ICU patients in comparison to floor patients). These markers were collected for exploratory analysis, not for decision making in the majority of cases, thus there was no uniform protocol for collecting markers. Overall, tracking markers may be useful in determining the severity of COVID-19 infection and ascertaining disposition. The effect of dexamethasone on inflammatory markers remains to be determined, as our cases are from before the RECOVERY trial.

Next steps in furthering this research include:

- Ascertain levels at which patients are more likely to be admitted to ICU or require mechanical ventilation (could also match markers with P:F ratios).
- Determine if there is a certain level at which steroids may be of benefit.
- Determine if these markers may be used to track duration of therapy and when therapy can be stopped.

References

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