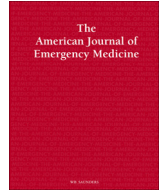




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Risk factors associated with hospital admission in COVID-19 patients initially admitted to an observation unit

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ARTICLE INFO

Article history:

Received 10 July 2020

Received in revised form 8 September 2020

Accepted 3 October 2020

Keywords:

COVID-19

Observation unit

Adverse outcomes

Risk stratification

ABSTRACT

Background: No set guidelines to guide disposition decisions from the emergency department (ED) in patients with COVID-19 exist. Our goal was to determine characteristics that identify patients at high risk for adverse outcomes who may need admission to the hospital instead of an observation unit.

Methods: We retrospectively enrolled 116 adult patients with COVID-19 admitted to an ED observation unit. We included patients with bilateral infiltrates on chest imaging, COVID-19 testing performed, and/or COVID-19 suspected as the primary diagnosis. The primary outcome was hospital admission. We assessed risk factors associated with this outcome using univariate and multivariable logistic regression.

Results: Of 116 patients, 33 or 28% (95% confidence interval [CI] 20–37%) required admission from the observation unit. On multivariable logistic regression analysis, we found that hypoxia defined as room-air oxygen saturation < 95% (OR 3.11, CI 1.23–7.88) and bilateral infiltrates on chest radiography (OR 5.57, CI 1.66–18.96) were independently associated with hospital admission, after adjusting for age. Two three-factor composite predictor models, age > 48 years, bilateral infiltrates, hypoxia, and Hispanic race, bilateral infiltrates, hypoxia yield an OR for admission of 4.99 (CI 1.50–16.65) with an AUC of 0.59 (CI 0.51–0.67) and 6.78 (CI 2.11–21.85) with an AUC of 0.62 (CI 0.54–0.71), respectively.

Conclusions: Over 1/4 of suspected COVID-19 patients admitted to an ED observation unit ultimately required admission to the hospital. Risk factors associated with admission include hypoxia, bilateral infiltrates on chest radiography, or the combination of these two factors plus either age > 48 years or Hispanic race.

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1. Introduction

A novel coronavirus (Coronavirus Disease 2019 or COVID-19) was first identified as a human pathogen in November of 2019 in China. At the time of the writing of this manuscript, the pandemic caused by this virus is still ongoing. The outbreak presents a significant threat to global health: rapidly spreading across the globe, and infecting millions of patients and killing hundreds of thousands, with numbers increasing on a daily basis [1–3]. The mortality rate from the disease has been estimated from 0.4% to 7% [4], and is widely recognized to be affected by age and comorbidity, with patients aged >70 and those with multiple

cardiovascular or pulmonary comorbidities being at exponentially higher risk of death [5–9]. While most patients who contract COVID-19 have mild symptoms initially, many of these patients develop severe symptoms 7–10 days into their illness [9,10].

Since patients present to the emergency department (ED) at any point during the spectrum of illness, it can be difficult to determine which patients require admission and which are safe for discharge. Some EDs utilize an observation unit, where patients continue to be observed and managed for an additional 24 h to decide if the patient ultimately needs admission to the hospital or is stable for discharge. Clinical decision aids can accurately identify patients at risk for a bad outcome. While some aids have been developed to identify severe cases of COVID-19 in already admitted patients [11,12], no studies have assessed lower risk patients in the ED. Thus, there remain no set criteria or recommendations to guide disposition in ED patients with or suspected COVID-19. If we could predict which patients will ultimately require hospital admission within 24 h of observation time, we would be able to more

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appropriately allocate resources from the onset, guide disposition decisions and potentially improve patient care.

The primary objective of this study was to determine risks factors associated with hospital admission in patients admitted to an ED observation unit with COVID-19 or suspected COVID-19.

2. Methods

2.1. Study design

This was a retrospective study of adult patients with suspected COVID-19 admitted to an ED observation unit over a 6-week period (3/11/20 to 4/20/20), during the peak COVID-19 surge experienced at our institution. Patients were enrolled from one large urban academic ED with an annual census of 105,000 patient visits. The ED observation unit has 12 staffed beds. During this time period around 1070 COVID or suspected COVID patients were seen in the ED, and 579 were admitted to the hospital. This study was approved by the Institutional Review Board.

We included all adult patients (>18 years old) who were admitted to the ED observation unit with any of the following: 1) bilateral infiltrates on chest imaging (radiography or computed tomography), 2) COVID-19 testing performed, and/or 3) COVID-19 suspected as the primary diagnosis as documented by the clinical team. We excluded patients discharged from the ED, admitted directly to the hospital, or admitted to the observation unit with a defined illnesses not related to COVID-19.

2.2. Study protocol

All patients admitted to the observation unit during the study timeframe were identified through a search in the electronic medical record (EMR). Patients were admitted to the observation unit for any number of reasons including dehydration, bilateral pneumonia, hypoxia, abnormal vital signs including tachycardia and tachypnea, inability to tolerate po, and dyspnea with exertion. Two blinded abstractors screened 50 charts to determine study inclusion/exclusion and Kappa for interrater reliability was calculated, $k = 0.92$ (confidence interval [CI] 0.811–1). Discrepancies were resolved by discussion and the remaining charts were divided and screened. Three physicians extracted data from the EMR following previously published methods for chart review [13]. Prior to data abstraction reviewers completed training to ensure all study variables were being collected in the same format. This training included how and where to abstract data from the EMR, how to complete the standardized data abstraction form, and reviewed study variable definitions. Periodic study monitoring was also performed. Reviewers were not blinded to the study hypothesis.

Data was input into a standardized data collection form in RedCap (Vanderbilt University, Nashville, TN). We collected demographic information, previously documented medical comorbidities, initial ED vital signs, lowest room air oxygenation saturation, ambulatory oxygenation saturation (if recorded), laboratory testing, imaging findings, treatment in the ED and observation unit, disposition and outcomes. All of these factors were analyzed as potential predictor variables. The primary outcome assessed potential risks factors associated with hospital admission in patients initially admitted to an ED observation unit with COVID-19 or suspected COVID-19. We also assessed the percentage of patients requiring hospital admission from the observation unit and mortality within 7 days of initial visit.

2.3. Data analysis

Descriptive statistics were calculated for patients requiring admission from the observation unit. Normality assumption was checked with the Shapiro-Wilk test; means (with standard deviations) and medians (with inter-quartile ranges) were calculated, as appropriate.

Means were compared with an unpaired *t*-test, medians with the Wilcoxon Rank-Sum Test, and bivariate frequencies with Pearson's Chi-Square or Fisher's Exact test, where appropriate. Univariate logistic regression (LR) was used to assess the association of demographic and clinical data with the primary outcome. Continuous predictors were dichotomized (rounded to the nearest whole number) with a cut-point determined by Youden's J statistic. To avoid introducing bias associated with complete case analysis, any variables with missingness >5% were excluded from consideration as predictors. Univariate predictors with a *p*-value <0.05 were then entered into a multivariable LR model to assess the independent contribution of each predictor. Additional candidate predictors were selected for assessment in the multivariable model based on a priori clinical plausibility of contributing to the primary outcome including age, history of cardiopulmonary disease, current smoker, and obesity (Body Mass Index [BMI] >30 kg/m²). Given the rapidly changing clinical environment and management recommendations during the pandemic, visit date was also assessed as a predictor in the multivariable model. To avoid over-fitting, an events-per-variable ratio of 10:1 was used. Final variable selection was based on comparison Akaike's Information Criteria, area under the receiver operating characteristic curve (AUC), and the Hosmer-Lemeshow test, amongst the candidate models. Three-component composite predictor variables, with candidates selected using the aforementioned criteria, were also constructed to assess the combined association of all predictors (i.e. predictor A and B and C) with the primary outcome. The two-tailed significance level was set at 0.05 for all comparisons. Given the exploratory nature of this study and the novelty of SARS-CoV-2 disease, a post-hoc power calculation was not performed. Statistical analysis was completed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

Two hundred and seventy-five patients were admitted to the observation unit during the study period. Of the 116 patients meeting inclusion criteria, 33 (28%, CI 20–37%) required admission to the hospital, see Fig. 1. The mean age was 52.6 years (SD 14.4, range 20–85 years), and the median duration of symptoms prior to evaluation was 7 days (IQR 7, range 0–30 days). African American and Hispanic patients represented a majority of the study population, 72%. Table 1 shows patient characteristics comparing patients who required hospital admission versus those who did not. Patients requiring hospital admission were more likely to be Hispanic, non-smokers and have a longer duration of symptoms (7 versus 5 days, *p* = 0.04).

Of the 33 patients who required hospital admission, 5 (15%) required admission to the intensive care unit during the course of their hospitalization. Two patients were admitted directly from the observation unit to the intensive care unit for hypoxic respiratory failure; one patient required a non-rebreather and the other non-invasive ventilation. The other 3 patients were initially admitted to the floor and later admitted to the intensive care unit requiring intubation for hypoxic respiratory failure. No patients died during their hospital stay or within

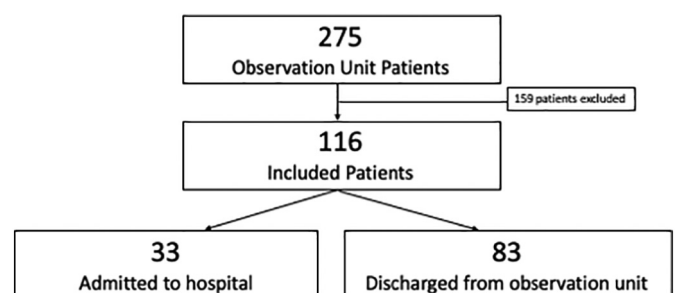


Fig. 1. Patient flow through study.

Table 1
Characteristics of patients requiring admission versus those discharged, $n = 116$

| | Admitted ($N = 33$) | Discharged ($N = 83$) | P-Value |
|-----------------------------|--------------------------|----------------------------|---------------|
| Age (years), Median (Range) | 52.4 (21–85) | 52.6 (20–81) | 0.9400 |
| Gender (%) | | | 0.4138 |
| Female | 14 (42.4) | 43 (51.8) | |
| Male | 19 (57.6) | 40 (48.1) | |
| Race | | | 0.014 |
| Black | 10 (30.3) | 36 (43.4) | |
| Hispanic | 18 (54.5) | 20 (24.1) | |
| White | 3 (9.0) | 20 (24.1) | |
| Other | 2 (6.1) | 7 (8.4) | |
| Metric BMI, Median (Q1, Q3) | 29.1 (25.6, 32.7) | 28.9 (25.0, 35.9) | 0.9500 |
| Symptom onset, days (range) | 7.0 (1–14) | 5.1 (0–30) | 0.0400 |
| Symptoms | | | |
| Shortness of breath | 26 (78.8) | 60 (72.3) | 0.6389 |
| Cough | 30 (90.9) | 68 (81.9) | 0.2707 |
| Fever | 19 (57.6) | 51 (61.5) | 0.8337 |
| Chest Pain | 8 (24.2) | 25 (30.1) | 0.6500 |
| Diarrhea | 6 (18.1) | 16 (19.2) | 1.0000 |
| Vomiting | 4 (12.1) | 14 (16.9) | 0.7767 |
| Co-morbidities | | | |
| Smoking | 2 (6.06) | 20 (24.1) | 0.0339 |
| Diabetes mellitus | 12 (36.4) | 24 (28.9) | 0.5061 |
| Hyperlipidemia | 9 (27.3) | 26 (31.3) | 0.6700 |
| Hypertension | 14 (42.4) | 44 (53.0) | 0.4107 |
| Heart Failure | 3 (9.0) | 6 (7.2) | 0.7124 |
| Ischemic Heart Disease | 1 (3.0) | 5 (6.0) | 0.6730 |
| Cancer | 3 (9.0) | 6 (7.2) | 0.7124 |
| COPD | 4 (12.1) | 13 (15.7) | 0.7751 |
| Asthma | 3 (9.0) | 14 (16.9) | 0.3885 |
| HIV/AIDS | 0 (0.0) | 2 (2.4) | 1.000 |
| Taking Immunomodulators | 0 (0.0) | 4 (4.8) | 0.5765 |
| Taking Chemotherapy | 0 (0.0) | 1 (1.2) | 1.000 |
| Taking Chronic Steroids | 0 (0.0) | 2 (2.4) | 1.000 |
| Obesity (BMI >30) | 14 (42.4) | 36 (43.4) | 1.000 |

P-values that are significant are bolded.

one week of their initial ED presentation. Eighty-three patients were discharged from the observation unit. Of these patients, 11 were discharged on supplemental oxygen. Nine (11%) patients returned to the ED within 7-days.

3.1. Testing and imaging

Sixty-eight (59%) of patients tested positive for COVID-19 by nasal swab polymerase chain reaction, 41 (35%) tested negative, and 7 (6%) were not tested. One hundred and twelve (97%) patients had chest imaging performed, 106 (95%) had a chest radiograph and 6 (5%) had computed tomography alone. Of these patients, 59 (53%) had multifocal infiltrates on chest imaging, 12 (11%) had single lobe (focal) findings, and 41 (37%) had no acute pulmonary findings.

3.2. Treatment

While in the ED and observation unit, 60 (52%) of patients were treated with antibiotics, 26 (22%) were treated with hydroxychloroquine, and 47 (41%) received supplemental oxygen.

3.3. Univariate analysis

On univariate LR analysis, the following characteristics were associated with an increased odds of admission from the observation unit: room-air oxygen saturation < 95% at any time during ED care (odds ratio [OR] 4.66, CI 1.96–11.10), chest x-ray (CXR) findings as interpreted by a board certified Radiologist (bilateral infiltrates versus clear, OR 7.29, CI 2.30–23.08 and unilateral versus clear, OR 3.08, CI 0.58–16.30; $p = 0.003$ for the overall association between CXR and admission), onset of symptoms >3 days (OR 3.17, CI 1.11–9.07). History of

cardiopulmonary disease (OR 0.38, CI 0.17–0.87), being a smoker (OR 0.20, CI 0.05–0.93), and non-Hispanic race (OR 0.31, CI 0.12–0.79 for Black versus Hispanic and 0.17, CI 0.04–0.66 for White versus Hispanic, respectively) were associated with reduced odds of admission. No other predictors were significantly associated with admission, including age and date or week of visit (data not shown).

3.4. Multivariable analysis

The final multivariable LR model included room-air oxygen saturation > 95% ([RA95] yes versus no), CXR findings (clear versus unilateral infiltrates versus bilateral infiltrates) and age (for the global null hypothesis that all ORs = 1, $p = 0.003$). While the independent effect of age was not statistically significant, it was retained in the model “by meaning” (i.e., given the weight this factor is given by clinicians when making admission decisions). The adjusted ORs from the final model are age (OR 1.0, CI 0.97–1.04), RA95 (OR 3.11, CI 1.23–7.88), and CXR result (bilateral infiltrates versus clear, OR 5.57, CI 1.66–18.96 and unilateral infiltrates versus clear, OR 2.77, CI 0.50–15.35); $p = 0.02$ for the overall association of CXR result with admission. AUC for the full model is 0.76, CI 0.66–0.86. Interactions between age and CXR result and age and RA95 were not significant and thus were not retained in the final model.

For the three-factor composite predictor of age > 48 (the optimal cut-point based on Youden's J statistic), bilateral infiltrates, and room-air oxygen saturation < 95% ($n = 13$), the OR for admission was 4.99 (CI 1.50–16.65) with an AUC of 0.59 (CI 0.51–0.67); for bilateral infiltrates, room-air oxygen saturation < 95%, and Hispanic race ($n = 15$), the OR for admission was 6.78 (CI 2.11–21.85) with an AUC of 0.62 (CI 0.54–0.71).

4. Discussion

Patients with COVID-19 present to the ED with varying degrees of illness [3]. Much of the prior published data regarding COVID-19 patients has focused on the severe side of the spectrum, for example determining risk factors for intensive care unit admission, mortality and mechanical ventilation [3,14–16]. However, disposition decisions from the ED in patients who are lower risk for adverse outcomes remains a challenge, with limited data and no current guidelines to help guide these decisions. Clinical decision aids, such as the Pulmonary Embolism Rule-out Criteria (PERC), utilize composite predictor variables to identify patients at higher or lower risk for a disease or outcome and their use can reduce practice variability [17].

In this study we evaluated a lower risk cohort of patients admitted to an observation unit. We found that over 1/4 of patients subsequently required hospital admission, with 3 of these patients requiring intubation for respiratory failure. Risk factors independently associated with admission on multivariable LR included hypoxia (room-air oxygen saturation < 95%), bilateral infiltrates on chest radiography, adjusted for age, with an AUC of 0.76, CI 0.66–0.86. This suggests that patients with either hypoxia or bilateral infiltrates on chest radiography (or both) have a high likelihood that they will require hospital admission—regardless of age—and thus may not be suitable for the observation unit.

Composite predictor variables offer the advantage of providing details on the effect of patients who meet all the component criteria, rather than the individual effects provided in multivariable models. A potential drawback, however, is that more complex composites may only capture a small number of patients (i.e., those who meet all criteria). Thus, we elected to limit our composite predictor to three components. For the three-factor composite predictors, bilateral infiltrates, hypoxia, and Hispanic race (OR for admission of 6.78 (CI 2.11–21.85), AUC of 0.62 (CI 0.54–0.71)) performed slightly better than the combination of age > 48, bilateral infiltrates, and hypoxia (OR for admission 4.99 (CI 1.50–16.65), AUC of 0.59 (CI 0.51–0.67)). This suggests that patients meeting either of the above composite predictor models have high

rates of treatment failure in the observation unit and supports a full admission for these patients. While the point estimate from the first composite predictor (bilateral infiltrates, hypoxia, and Hispanic race) is greater than the independent ORs from the multivariable model, the AUC from the latter is greater. Thus the multivariable model, which correctly classifies a greater proportion of patients, likely represents a more efficient approach.

This study differs from prior literature finding that cardiovascular co-morbidities such as heart failure, coronary artery disease, type 2 diabetes and obesity were associated with increased illness severity [14,16,18,19]. In our study we did not find these risk factors to be significant for those patients with more severe disease who required admission. In fact we found on univariate analysis that history of cardiopulmonary disease was associated with reduced odds of admission, however this did not hold true on multivariate analysis. To account for the differences between our study and prior studies, it is possible that our patient sample was too small to see a difference or more likely that patients who were directly admitted from the ED (which were excluded from this study) were more likely to have these associated medical co-morbidities.

Zhou et al. [11] found that older age was associated with in-hospital mortality on multivariable regression analysis with an OR of 1.1 (95% CI 1.03–1.17). In our study age was not statistically significantly associated with need for hospital admission, however, it was retained in the model “by meaning” as the age of a patient is a strong factor weighed by clinicians when making admission decisions. The median age of included patients was 52 years with a range of 20 to 85 years old. It is likely that most older patients were directly admitted from the ED and thus excluded from this analysis. When taking into account age > 48, as determined to be the optimal cut-point based on Youden's J statistic, in addition to bilateral infiltrates on CXR and hypoxia (oxygen saturation < 95%) the likelihood of needing admission is high (OR 4.99).

Prior data has shown mixed evidence with regards to smoking status whether it is associated with disease severity and worse outcomes [20,21]. Interestingly, in our study we found that patients who were non-smokers were more likely to require admission when compared to smokers ($p < 0.05$). However, this did not remain significant on multivariable analysis. It is therefore probable that other confounding factors explain this association, although we did not explore exactly what other factors accounted for this.

We found that length of disease, on univariate analysis, was associated with an increased odds of admission. Greater than 3 days of illness had an OR of 3.17, CI 1.11–9.07. This is similar to prior studies showing that patients develop severe symptoms later in their disease course, typically after 7–10 days [11,15]. However, this did not remain significant on multivariable analysis.

As we learn more about management and disposition of low risk ED patients presenting with presumed COVID-19 it is important to recognize risk factors associated with hospital admission to guide disposition decisions. In this study we found a high rate of treatment failure in patients initially admitted to an observation unit. Risk factors independently associated with admission included hypoxia and bilateral infiltrates on chest radiography, while the combination of these factors with either age > 48 or Hispanic race were likewise associated with admission. Future larger prospective studies are needed to potentially develop a decision tool to help guide disposition decisions from the ED.

4.1. Limitations

The study has several important limitations. This was a descriptive study with no comparison group, so our findings cannot determine any definitive association with changes in outcomes. Our screening criteria could have excluded some patients who were in the observation unit with suspected COVID-19. During this time, our institution had a limited supply of test kits and set guidelines as to who qualified for testing. Patient who were younger with no comorbid conditions were often

not tested due to these guidelines. These patients could have been excluded if the ED clinician and the observation unit clinician did not explicitly note concern for COVID-19. Furthermore, patients who did not have a documented concern for COVID-19, no COVID-19 testing ordered, and had unilateral or clear CXR findings could have been excluded as well. We assume these cases are rare due to the heightened concern during the study period leading to increased documentation regarding COVID-19. Additionally, we found a high interrater reliability between two blinded reviewers for patient inclusion/exclusion making it less likely we missed any patients who should have been included for analysis.

As this was a retrospective chart review the decision to admit to the observation unit, admit to the inpatient unit or discharge was done entirely at the providers' discretion. Most of these patients were likely admitted as they were in a disposition “grey-zone” and providers likely felt an additional 24-h period would assist in their ultimate disposition. However, we realize that providers have different practice patterns and we could have included patients who would have been discharged or admitted if seen by another provider. In addition, the decision to admit a patient from the observation unit takes into account multiple patient, provider and hospital factors, and differs from clinician to clinician [22,23]. However, all 33 patients requiring admission to the hospital in this study were admitted for worsening respiratory status.

The decision to order labs and radiographs was completely dependent on the provider. Our observation unit does require basic laboratory investigations (BMP, CBC) and often a CXR in those patients with respiratory complaints, but other labs such as d-dimer, LDH were provider dependent. We assume patients deemed higher risk for more severe disease had more labs drawn, but this assumption may not have always been true.

This study included patients from a single center over 6 weeks. While this period was during the peak COVID-19 surge experienced at our institution, it does only represent a subset of patients from one ED during a finite period of time. Additionally, these data were collected from a large urban academic county ED, which may limit generalizability.

5. Conclusion

In this small retrospective study of patients with confirmed or suspected COVID-19 we found that over one-quarter of presumed lower risk patients initially admitted to an ED observation unit ultimately required admission to the hospital. Irrespective of age, room-air oxygen saturation < 95% or bilateral infiltrates on CXR were associated with increased risk of admission (OR 3.11 [CI 1.23–7.88] and OR 5.57 [CI 1.66–18.96], respectively). Two predictor models for admission included: 1) age > 48, bilateral infiltrates and hypoxia (OR 4.99, AUC of 0.59, CI 0.51–0.67), and 2) Hispanic race, bilateral infiltrates and hypoxia (OR 6.78, AUC of 0.62 (CI 0.54–0.71)). This data supports that patients with these findings may require hospital admission as they have a high failure rate in the observation unit.

Funding sources/disclosures

N/A.

Prior presentations

None.

Author contributions

FMR was responsible for concept, data collection, interpretation, writing, revising, approval, study supervision, and takes responsibility for paper as a whole. AW was responsible for data collection, interpretation, writing, revising, and study supervision. RE was responsible for

data analysis, interpretation, writing, revising. JJ, AC and CL were responsible for data collection, interpretation, and writing and revising.

Declaration of Competing Interest

None.

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