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Assessing the need for transfer to the intensive care unit for Coronavirus-19 disease: Epidemiology and risk factors

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ABSTRACT

Background: Although many patients with coronavirus disease 2019 (Covid-19) require direct admission to the intensive care unit (ICU), some are sent after admission. Clinicians require an understanding of this phenomenon and various risk stratification approaches for recognizing these subjects.

Methods: We examined all Covid-19 patients sent initially to a ward who subsequently required care in the ICU. We examined the timing transfer and attempted to develop a risk score based on baseline variables to predict progressive disease. We evaluated the utility of the CURB-65 score at identifying the need for ICU transfer.

Results: The cohort included 245 subjects (mean age 59.0 ± 14.2 years, 61.2% male) and 20% were eventually sent to the ICU. The median time to transfer was 2.5 days. Approximately 1/3rd of patients were not moved until day 4 or later and the main reason for transfer (79.2%) was worsening respiratory failure. A baseline absolute lymphocyte count (ALC) of $\leq$0.8 10^3/ml and a serum ferritin $\geq$1000 ng/ml were independently associated with ICU transfer. Co-morbid illnesses did not correlate with eventual ICU care. Neither a risk score based on a low ALC and/or high ferritin nor the CURB-65 score performed well at predicting need for transfer.

Conclusion: Covid-19 patients admitted to general wards face a significant risk for deterioration necessitating ICU admission and respiratory failure can occur late in this disease. Neither baseline clinical factors nor the CURB-65 score perform well as screening tests to categorize these subjects as likely to progress to ICU care.

1. Introduction

The coronavirus disease 19 (Covid-19) pandemic caused by the SARS CoV-2 virus has resulted in substantial morbidity and mortality. This infection has placed considerable burdens on acute care hospitals, generally, and on intensive care units (ICUs), specifically. Prior reports suggest that approximately 15% of those infected require admission to the hospital while more than 5% may need care in an ICU [1,2]. For those admitted to the ICU, the majority undergoes mechanical ventilation (MV) and the prevalence of Acute Respiratory Distress Syndrome (ARDS) is high [3]. Because of the strain placed on ICUs by the pandemic, multiple public health interventions have focused on containing the spread of SARS CoV-2 so as to constrain the exponential demand for ICU care. In essence, limitations in ICU resources have contributed to the logic underlying the concept of "flattening the curve." As a corollary, understanding the need for ICU care in Covid-19 has become a public health priority. Hence, a better appreciation of who might require ICU admission could facilitate efforts at disease modeling and public health policy. At the same time, identifying variables that identify subjects who require transfer to an ICU could also help clinicians risk stratify and triage patients as they present with their acute infections.

For many other diseases that regularly necessitate admission to the ICU, various risk stratification tools exist. For example, for community-acquired pneumonia, both the Pneumonia Severity Index (PSI) and the CURB-65 score represent well-validated paradigms for risk stratification [4,5]. Researchers have developed other similar scores for conditions such as congestive heart failure and pulmonary embolism [6,7]. The existence of these tools has substantially facilitated triage decision-making when patients present to the hospital and has helped to insure individuals are sent to the correct level of care.

With respect to Covid-19, several studies have attempted to examine variables associated with need for ICU care [8.9]. These models, though, generally evaluate all patients presenting to the hospital. However, a

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crucial question revolves around identifying patients initially felt stable for admission to the general wards with Covid-19 but who then deteriorate and require an escalation of care and transfer to the ICU. To comprehend the actual potential need for ICU beds along with the desire to confidently admit subjects to a non-ICU floor, physicians require an understanding of the risk for deterioration among Covid-19 subjects sent, on presentation, to a medical ward.

To address these issues, we conducted a retrospective study of all subjects with Covid-19 admitted to our hospital in order a) to describe the epidemiology of needing transfer to the ICU subsequent to initial admission to the floor and b) to develop a risk tool to categorize these subjects based on variables accessed at time of original hospital presentation.

2. Materials and methods

2.1. Overview and subjects

We conducted a retrospective analysis of all consecutively admitted patients to our hospital diagnosed with Covid-19. Covid-19 was diagnosed based on a combination of appropriate clinical symptoms and the presence of SARS-CoV-2 in an upper or lower respiratory specimen. All testing was performed using a real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay. We excluded patients initially admitted directly to the ICU. We also excluded subjects who had a medical order limiting an escalation of care and thus precluding any transfer to a higher level of care. Subjects were admitted to our institution between March 17, 2020 and April 17, 2020. The Medstar Health Research Institute Institutional Review Board approved this study.

2.2. Endpoints

Need for transfer to the ICU represented our primary endpoint. The decision to admit to the ICU was left to a patient's primary physician and the ICU triage physician. The need for mechanical ventilation and/or treatment with vasopressors mandated movement to the ICU. The timing of admission to the ICU after floor admission served as a secondary endpoint as did the reason for transfer.

2.3. Variables

We collected information regarding patient demographics, underlying co-morbid illnesses, and baseline laboratory values. Specifically we assembled information regarding age, gender, and race. Co-morbidities of interest included the presence of underlying lung disease, such as asthma and/or chronic obstructive pulmonary disease (COPD). We also recorded if a patient had hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), or diabetes mellitus (DM). We further noted if a patient was undergoing active chemotherapy for malignancy, carried a diagnosis of human immunodeficiency virus (HIV) infection, or required chronic hemodialysis. With respect to laboratory testing done at the time of hospital admission, we explored the absolute lymphocyte count (ALC) along with the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Other variables evaluated included the serum D-dimer, lactate dehydrogenase, and ferritin. Each of variables eventually recorded was selected prior to data collection based on a biologically plausible link with a need for escalation of care.

2.4. Risk stratification

We calculated a CURB-65 score for each patient based on clinical and lab values available at presentation [5]. We defined confusion, in accordance with the approach of others, as a Glasgow Coma Score (GCS) of <14 [10]. Additionally we developed a novel risk score based on a logistic regression model exploring variables independently associated with an escalation of care. (see below).

2.5. Statistics

We compared categorical variables with the Fisher's exact test and continuous variables with either Student's t-test or the Mann Whitney *U* test, as appropriate. All tests were two tailed and a p value of <0.05 was considered to represent statistical significance.

To determine factors independently associated with transfer to the ICU after admission to the ward, we relied on logistic regression. The regression was a step-wise backwards approach, and we entered all variables significant at the 0.15 level in univariate analysis into the model. Variables were assessed for co-linearity. We assessed goodness of fit with the Hosmer-Lemeshow (HL) test. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) are presented where appropriate.

From the logistic regression findings, we created a predictive scoring tool to identify persons with Covid-19 later admitted to the ICU. We converted the β coefficients from the logistic regression into whole integers, after mathematical simplification, representing points and then summed these points to calculate a total score. We then explored the predictive value of the point score at correctly indicating the need for escalation of care via a receiver operating characteristic (ROC) curve. We compared the predictive accuracy of the CURB-65 score and our novel risk score via comparing areas under the ROC curves (AUROCs).

All analyses were conducted with SPSS (v 25.0, IBM, Armonk, NY).

3. Results

The final cohort included 245 subjects (mean age 59.0 ± 14.2 years, 61.2% male). Subsequent to admission to the floor, 48 patients (19.6%) were transferred to the ICU. The median time to ICU transfer was 2.5 days. While more than half (54.2%) of patients were moved to intensive care within 48 h of admission, 33.3% were not transferred until hospital day 4 or later. The main reason for movement to the ICU was progressive respiratory failure (79.2%) and did not differ between those moved within 48 h of presentations or subjects sent to the ICU after a floor length of stay of more than 2 days (84.0% vs. 73.9%, p = 0.478). Thirty-two (66.6%) of those transferred eventually required mechanical ventilation (MV). Of these individuals placed on MV, 12 required immediate intubation while 20 failed efforts with either non-invasive ventilation (NIV) and/or high-flow oxygen. Of the 16 persons moved to the ICU who never needed MV, 10 were treated with NIV and/or high-flow oxygen. Patients sent to the ICU from the floor accounted for approximately 35% of all patients requiring ICU care during the study period.

Table 1 reveals the baseline characteristics of the patients. There was no difference in age or demographic characteristics between patients able to remain on the floor as opposed to needing ICU transfer. Similarly, in univariate analysis, no co-morbid illness was statistically associated with escalation of care. We did observe a trend in the need for admission to the ICU among patients with underlying active malignancy (OR: 2.42, 95% CI: 0.91–2.42).

In contrast to the results for co-morbidities, we noted several differences in admission lab values (Table 1.) as they relate to the need for moving to a higher level of care. For example, there was a trend towards an ALC of $\leq$0.8 10^3/ml being more prevalent in persons sent to the ICU. We further documented that a high ferritin ($\geq$1000 ng/mL) transpired more often (OR: 2.33, 95% CI: 1.11–4.90, p = 0.037) as did greater elevations in serum LDH ($\geq$500 u/L) in the cohort moved to an ICU. Specifically, an elevated LDH occurred 3 times more often in the transferred cohort (OR: 2.99; 95% CI: 1.35–6.65, p = 0.010). A diagnosis of an active malignancy was not retained in the model.

Table 2 shows the results of the logistic regression. Two variables remained independently associated with subsequent ICU transfer. Patients with a baseline ALC $\leq$0.8 10^3/ml were twice as likely to be escalated to the ICU (AOR: 2.11, 95% CI: 1.01–4.39, p = 0.047). An initial serum ferritin $\geq$1000 ng/mL also was independently linked to later ICU admission (AOR: 2.65, 95% CI: 1.73–5.74, p = 0.013). The

Table 1
Baseline characteristics.

Variable	ICU Transfer (n = 48)	Remained on Floor (n = 197)	P
Demographics			
Age, years, ±SD	59.1 ± 16.9	58.9 ± 13.4	0.953
Male, %	51.5%	63.3%	0.152
Race			0.526
-African American, %	70.4%	71.4%	
-Hispanic, %	16.3%	17.2%	
-Other, %	10.2%	10.2%	
-Caucasian, %	3.1%	6.1%	
Co-morbidities			
Asthma, %	12.2%	15.8%	0.658
COPD, %	8.2%	4.6%	0.299
CAD, %	6.1%	9.2%	0.778
HTN, %	63.3%	59.7%	0.745
CHF, %	14.4%	9.2%	0.723
DM, %	20.8%	17.9%	0.384
HIV, %	4.1%	2.0%	0.345
Cancer, %	14.3%	6.6%	0.087
ESRD, %	4.1%	3.1%	0.662
Lab values			
ALC, 10^3/μL, ±SD	1.2 ± 0.6	1.3 ± 0.9	0.737
ALC ≤0.8 10^3/μL, %	26.7%	17.4%	0.119
ESR, mm/hr, ±SD	64.1 ± 22.1	63.9 ± 25.2	0.937
CRP, mg/L, ±SD	94.8 ± 177.1	106.1 + 52.9	0.692
D Dimer, mcg/ml, ±SD	1.9 ± 3.1	3.0 ± 5.2	0.210
D Dimer ≥ 2 mcg/ml	38.8%	46.4%	0.422
Ferritin, ng/mL ±SD	884.4 ± 1695.3	1165.5 + 1608.6	0.271
Ferritin ≥1000 ng/mL, %	35.7%	19.3%	0.037
LDH u/L, ±SD	371.9 ± 299.5	422.5 ± 199.0	0.307
LDH ≥ 500 u/L, %	31.7%	13.4%	0.010

Abbreviations: ALC- absolute lymphocyte count, CAD – coronary artery disease, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease, CRP – C reactive protein, DM – diabetes mellitus, ESR – erythrocyte sedimentation rate, ESRD – end stage renal disease, HIV – human immunodeficiency virus, HTN - hypertension, LDH - Lactate dehydrogenase, SD – standard deviation.

Table 2
Independent variables associated with intensive care unit transfer.

Variable	95% Confidence Interval	Adjusted Odds Ratio	p value
ALC ≤0.8 10^3/mL	1.01–4.39	2.11	0.047
Ferritin ≥1000 ng/mL	1.73–5.74	2.65	0.013

AbbreviationsSee Table 1.

model had a final Hosmer-Lemeshow p value of 0.813 suggesting good fit.

In terms of risk prediction tools, the median CURB-65 score was 1. Fig. 1 displays the relationship between initial CURB-65 score and later ICU transfer. This relationship was not statistically significant ($p = 0.228$). For our novel risk score, one point each was assigned based on the presence of an ALC ≤0.8 10^3/ml and/or a serum ferritin ≥1000 ng/mL – for a maximum score of 2. As shown in Fig. 2, as this score increased, so too did the risk for ICU transfer ($p = 0.005$). For example, in those patients with a score of 0 and, thus lacking either criterion, only approximately 13% were eventually admitted to an ICU. Alternatively, nearly 35% of subjects meeting both criteria ultimately needed ICU level care. Despite this finding, neither scoring paradigm performed well as a screening test for post-admission need for ICU transfer. Specifically, the AUROC for the novel score equaled 0.630 (95%CI: 0.545–0.725). For CURB-65, the AUROC was 0.522 (95% CI: 0.457–0.655). These AUROCs were not statistically different.

4. Discussion

This retrospective analysis indicates that nearly one in 5 patients with Covid-19 infection who are admitted to the floor upon hospital presentation will deteriorate and need transfer to the ICU. Many of those sent to the ICU subsequently require MV, even despite efforts to employ NIV and/or high flow oxygen. The timing of escalation of care is not confined to the early period following initial hospitalization. Rather, it appears that subjects are at risk for declining during the entire length of their stay on a general ward. Co-morbid illnesses are not associated with the risk for ICU transfer while two initial lab values (ALC ≤0.8 10^3/ml and ferritin ≥1000 ng/mL) identify those at higher risk for ICU admission. Nonetheless, neither a model based on these lab measures nor the CURB-65 score represents an adequate risk stratification rubric given the limited sensitivity and specificity of these systems.

Our finding that a significant proportion of patients on the floor will need eventual ICU care is important. Policy makers and health planners must recognize that estimated ICU bed demand will vary not only as a function of patients directly admitted to the ICU from the emergency department but also based on the burden of Covid-19 on non-ICU wards [11–13]. A strategy that estimates ICU bed needs that fails to consider the impact of the floor Covid-19 population will likely misjudge demand and lead to potential crowding and delays in timely ICU transfer. Similarly, as health systems attempt to load balance and move Covid-19 patients from one institution to another, leaders of these efforts must consider, before shifting patients, the surge capacity of the receiving hospitals' ICUs – even though these transferred patients are specifically being sent to the wards. Not surprisingly, progressive respiratory failure represents the key reason for ICU transfer. That this risk does not seem to diminish in the early days after ward admission stresses the need for

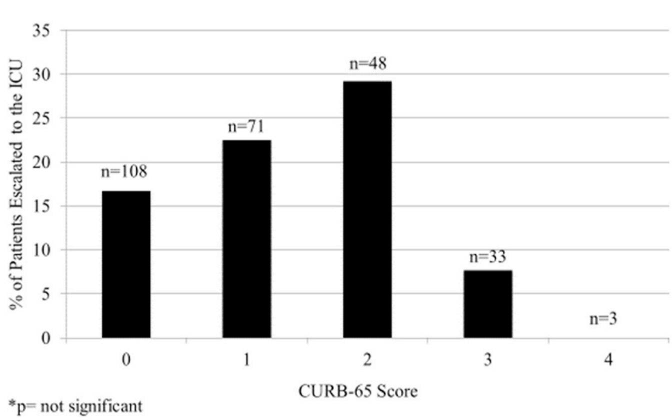

Fig. 1. Relationship between CRUB-65 Score and need for escalation of care.

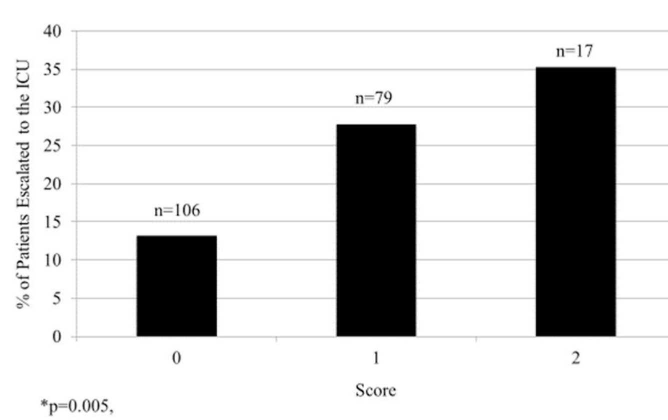

Fig. 2. Relationship between novel risk score and need for escalation of care.

vigilance on the part of clinicians and underscores that there does not appear to be some window beyond which a patient is free from a need for MV in Covid-19. Our findings emphasize this point in that the use of NIV and/or high flow oxygen may not prevent the need for eventual MV in those who become so severely ill as to need care in the ICU. At the same time, this observation indicates that planners must consider both having a sufficient number of ventilators but also review potential greater demand for other respiratory support devices such as those that can deliver NIV and high flow oxygen.

Our study is unique in that it looks specifically at those with Covid-19 who are initially thought stable. Prior accounts of Covid-19 patients that discuss disease severity have generally addressed those needing either ICU care or MV at the time of coming to the hospital [1,2]. For example, Huang and colleagues describe outcomes in Covid-19 infection and report the proportion of patients ever needing ICU care but do not delineate whether these patients were directly sent to the ICU from the emergency department or later moved after being on the ward [2]. Similarly, in an analysis of 249 patients diagnosed with Covid-19, Chen and co-workers relate disease progression over time [8]. Although they discern that nearly 10% of the population spent time in their ICU, they fail to note the source of these admissions. In a more detailed description of ICU subjects, Du et al. present information related to cause of death while in the ICU but neglect to comment on how or when a patient came to be in the ICU [1,3]. In essence, the emphasis of many reports thus far has been either on the initially critically ill population with Covid-19 or those briefly hospitalized who recover quickly. This has left undescribed a core group with Covid-19 who might later come to need more aggressive care. Furthermore, hospitalists and others treating Covid-19 outside the ICU certainly would benefit from an better awareness of the potential the degree to which such persons might subsequently decline. Our results, therefore, help to shed insight on this topic.

Other analyses have explicitly examined risk factors associated with disease progression in an effort to create risk stratification tools. Gong et al., for instance, developed a nomogram based on 372 patients designed to assess progression to severe Covid-19 [14,15]. Likewise, Dong and colleagues constructed a risk score based patient age, co-morbidities, ALC, and LDH to estimate onset of severe disease after being classified as “stable.” The present analysis contrasts with these two efforts in several ways. First, both Gong et al. and Dong et al. do not specifically explore need for ICU care. Second, their definitions of “severe disease” encompass a diverse set of variables that actually represent a range in disease acuity [14,15]. For example, both sets of investigators consider severe infection present if the patient develops any of the following: a respiratory rate $>$ 30 breath/minute, a resting oxygenation saturation of $\leq$93%, progresses to MV, or meets the clinical criteria for ARDS [14,15]. The implications for patient mortality vary greatly with ARDS vs. having a marginal oxygen saturation while not on a ventilator. Therefore, it is unclear if the pooled definition of “severe” employed by these authors is appropriate. Additionally, these researchers do not provide a breakdown of how many subjects met the criteria for the “severe” classification based on the unique components of their pooled endpoint. Hence, it is difficult to interpret their findings and consider how to apply them. Third, since the availability of ICU resources varies across the globe, it remains unclear if observations from Asia or Europe are applicable to the United States and vice versa. Hence, our observations help to describe a scenario where there is likely greater ICU bed availability.

Our inability to create a risk score with good sensitivity and specificity is not completely unanticipated. The current understanding of Covid-19 is rapidly changing, and thus there are likely important and nuanced variables that might identify the declining patient which the medical community has yet to appreciate. Moreover, that patients appear to be at risk for needing ICU care throughout their hospital stays likely explains why factors assessed at presentation have limited predictive value. Rather, some dynamic assessment of changes in parameters over time may prove more effective. In that same vein, CURB-65 was created to assess risk for mortality based on initial presentation in community-acquired pneumonia. Given that this tool was never calibrated to look at the ensuing need for ICU care, it seems logical to conclude that it would not perform well for this purpose.

The value of various biomarkers as either stand alone risk stratification tools or their use as part of some risk score is unclear. No biomarker proved effective at predicting need for patient transfer. Nonetheless, whether analyzed as a continuous or a categorical variable, all biomarkers were generally worse in those need transfer. Perhaps, with a larger sample size, we might have been able to identify one or two laboratory tests that could have facilitated decision making and identified subjects at high risk for decompensation. Certainly, future efforts should explore if measures such as D-dimer and the like can aid in the triage decision making process.

This study has a number of important limitations. First, its retrospective design exposes it to various forms of bias. We attempted to reduce the impact of bias by looking at specific endpoints where ascertainment is fairly straightforward. Concomitantly, the reliance on a step-wise logistic regression raises concerns regarding testimation biase. That we selected candidate variables prior to model creation should have limited the impact of this concern. Second, as our findings derive from a single center in a major urban setting in the United States they lack generalizability. Third, there are likely patients with Covid-19 who were not included because they presented to the hospital with a syndrome of acute respiratory infection before testing was more prevalent. Fourth, our sample size was limited. Although comparable in size to other reports thus far, our ability to detect important differences in baseline variables was reduced due to issues of statistical power. Larger studies with more diverse populations will be required to create risk stratification schemes. As a corollary, the size of our cohort precluded an effort at internal validation. Similarly, we did not perform any external validation as would be needed before the broad adoption of any scoring tool. Finally, the decision regarding transfer was otherwise not prospectively standardized and left to individual clinicians.

In conclusion, patients with Covid-19 admitted to general medical wards face a significant risk for clinical deterioration necessitating transfer to the ICU. Neither baseline clinical factors at time of presentation to the hospital nor the CURB-65 score perform well as screening tests to categorize these subjects likely to progress to needing ICU care.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

AFS and ESO are the guarantors of and take responsibility for the data and analysis and all coauthors take responsibility for the content of the manuscript. All authors have made substantial contributions to conception, design, analysis, and interpretation of data; drafted the submitted article or revised it critically for important intellectual content; provided final approval of the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declaration of competing interest

The authors have no competing interests relative to the topic of this manuscript.

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