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Early detection of hospitalized patients with COVID-19 at high risk of clinical deterioration: Utility of emergency department shock index

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ABSTRACT

Background: The COVID-19 outbreak has put an unprecedented strain on Emergency Departments (EDs) and other critical care resources. Early detection of patients that are at high risk of clinical deterioration and require intensive monitoring, is key in ED evaluation and disposition. A rapid and easy risk-stratification tool could aid clinicians in early decision making. The Shock Index (SI: heart rate/systolic blood pressure) proved useful in detecting hemodynamic instability in sepsis and myocardial infarction patients. In this study we aim to determine whether SI is discriminative for ICU admission and in-hospital mortality in COVID-19 patients.

Methods: Retrospective, observational, single-center study. All patients ≥18 years old who were hospitalized with COVID-19 (defined as: positive result on reverse transcription polymerase chain reaction (PCR) test) between March 1, 2020 and December 31, 2020 were included for analysis. Data were collected from electronic medical patient records and stored in a protected database. ED shock index was calculated and analyzed for its discriminative value on in-hospital mortality and ICU admission by a ROC curve analysis.

Results: In total, 411 patients were included. Of all patients 249 (61%) were male. ICU admission was observed in 92 patients (22%). Of these, 37 patients (40%) died in the ICU. Total in-hospital mortality was 28% (114 patients). For in-hospital mortality the optimal cut-off SI ≥ 0.86 was not discriminative (AUC 0.49 (95% CI: 0.43–0.56)), with a sensitivity of 12.3% and specificity of 93.6%. For ICU admission the optimal cut-off SI ≥ 0.57 was also not discriminative (AUC 0.56 (95% CI: 0.49–0.62)), with a sensitivity of 78.3% and a specificity of 34.2%.

Conclusion: In this cohort of patients hospitalized with COVID-19, SI measured at ED presentation was not discriminative for ICU admission and was not useful for early identification of patients at risk of clinical deterioration.

1. Background

The rapid worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting COVID-19 pandemic has placed an unprecedented strain on healthcare facilities in many countries. Apart from the considerable surge of patients requiring emergency department (ED) assessment, approximately 17% to 35% of hospitalized patients with COVID-19 require treatment in an intensive care unit (ICU) [1,2]. Although the majority of patients experience only mild or even no symptoms, up to 20% develop severe or critical disease [2-4]. Admission decisions are therefore largely based on clinical gestalt,

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comorbidities, respiratory function and hemodynamic parameters. Early detection of patients that are at high risk for clinical deterioration and who require intensive monitoring, is key in ED evaluation and disposition. A rapid and easy risk-stratification tool could aid clinicians in early decision making, which may prevent adverse patient outcomes. Such tools are currently lacking.

The shock index (SI), defined as heart rate (HR) divided by systolic blood pressure (SBP), can be easily calculated and has proven to be useful to detect hemodynamic instability in patients with sepsis and myocardial infarction [5-7]. Furthermore, it has shown to be predictive for hospital admission and in-hospital mortality [5,7]. In healthy adults, the SI ranges between 0.5 and 0.7 [8]. In ED patients presenting with infection, a normal SI (<0.7) and the absence of elevated lactate levels indicated a very low risk for severe sepsis at presentation [5]. In patients with acute circulatory failure, a SI ≥ 1 was associated with significantly poorer outcomes [9]. Likewise, a SI ≥ 1 in patients with pulmonary embolism was associated with higher in-hospital mortality [10].

The aim of this study was to assess the discriminative value of the SI on in-hospital mortality and ICU admission in COVID-19 patients in the ED who require hospitalization.

2. Methods

2.1. Study design

This was a retrospective, observational, single-center study in a teaching hospital in the Netherlands. The hospital is situated in a region with a high prevalence of COVID-19, with COVID-19 admission rates ranging from 90 to 330 per 100.000 inhabitants [11]. All patients ≥18 years old who were hospitalized with COVID-19 (defined as positive PCR test) between March 1, 2020 and December 31, 2020 were included for analysis. Exclusion criteria were: age under 18 years, inter-facility transfer of patients initially admitted to another hospital and previous refusal to participate in scientific research.

The study was approved by the institutional review board of VieCuri Medical Center (#602, May 18, 2020). Due to the retrospective and observational approach of the study a waiver of informed consent was provided.

2.2. Data collection and outcome measures

Data were collected from the electronic medical patient records. They were anonymously coded and stored in an online database (Castor Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands). Data collected included age, sex, medical history, medication use, symptoms and onset, clinical parameters in the ED, laboratory and microbiology testing and therapy (iv fluids, medication and oxygen). Follow up ended at discharge from the hospital or death.

SI was retrospectively calculated from the first SBP and HR measurements of the ED visit and analyzed for its discriminative value on the primary outcome measures: in-hospital mortality and ICU admission.

2.3. Statistical analysis

Baseline characteristics of included patients were presented as means with standard deviation (SD), median with interquartile range (IQR) or percentages. To determine the discriminative value of the SI on the outcome measures, a Receiver Operating Characteristic (ROC) curve analysis was used. Subsequently, an Area Under the Curve (AUC) was calculated, including a 95% confidence interval (95% CI) and Likelihood Ratio's (LRs). The optimal cut-off point for specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) was estimated using the Youden method. These calculations were performed online via http://www.biosoft.hacettepe.edu.tr/easyROC/. This study was sufficiently powered to estimate a specificity of 90–95% and sensitivity between 60 and 80% for outcomes with a prevalence of 20%, which was the estimated probability of ICU admission and in-hospital mortality in the study population. LR+ of at least 6.0 could be shown with the sample size of this study.

3. Results

Between March 1, 2020 and December 31, 2020, 411 patients with COVID-19 were hospitalized. Baseline characteristics are presented in Table 1. Of these, 249 (61%) were male. Median age was 72 years (IQR 61–80, range 24–93) and mean BMI was 28.14 (SD 5.31). Hypertension was the most commonly noted comorbidity (53%), followed by chronic cardiac disease (32%), obesity (30%), diabetes (27%) and chronic pulmonary disease (22%). Beta blockers or other heart rate modifying medications were used by 160 patients (39%). The median duration of symptoms until ED presentation was 7 days (IQR 4–10). Ninety-two patients (22%) were admitted to the ICU during the course of the disease. Of these, 37 patients (40%) died. The mean interval between admission and ICU admission was 2.21 days (SD 2.42). Median length of stay was 6 days (IQR 3–11, range 1–164). Total in-hospital mortality was 28% ($n = 114$); 72% ($n = 297$) were discharged alive of which 28 patients (10%) were transferred to a rehabilitation facility.

Eight out of 411 patients (<2%) had a SI ≥1 in the ED. Three of these patients were diagnosed with sepsis, two patients had a supraventricular tachycardia, one was pregnant, one was severely dehydrated and one had an intracardial lymphoma causing hemodynamic instability. Two of these patients died and two other patients were admitted to the ICU.

By means of a ROC analysis an optimal cut-off point of 0.86 was obtained for the SI concerning in-hospital mortality. The estimated sensitivity, specificity and PPV and NPV are outlined in Table 2. The estimated AUC was 0.49 (95% CI: 0.43–0.56) with a positive LR of 1.92 (1.00–3.70) and negative LR of 0.94 (0.87–1.01). The ROC analysis is shown in Fig. 1. Thirty-three patients (8%) had a SI ≥ 0.86, of which 14 died (42%) and 11 were admitted to the ICU (33%).

Table 1
Baseline characteristics

Total patients, N (%)	411 (100)
Male sex, N (%)	249 (61)
Mean Age (IQR)	72 (61–80)
Age, Range	24–93
Mean BMI (SD)	28.14 (5.31)
Comorbidities, N (%)	
Chronic Cardiac Disease	130 (31.6)
Chronic Pulmonary Disease	89 (21.7)
Chronic Kidney Disease	71 (17.3)
Liver Disease	2 (0.5)
Chronic Neurological Disorder	53 (12.9)
Malignant Neoplasm	48 (11.7)
Chronic Hematologic Disease	19 (4.6)
Obesity	123 (29.9)
Diabetes	110 (26.8)
Rheumatologic Disorder	54 (13.1)
Dementia	19 (4.6)
Hypertension	216 (52.6)
Heart rate modifying drugs, N (%)	160 (39)
Mean SI at admission (SD)	0.65 (0.17)
ICU admisssion, N (%)	92 (22)
Mean interval between admission and ICU (SD)	2.21 (2.42)*
ICU mortality, N (%)	37 (40)
Total in-hospital mortality, N (%)	114 (28)
Discharged alive – home, N (%)	269 (65)
Discharge alive – Rehabilitation, N (%)	28 (7)
Median duration of symptoms until ED presentation (IQR)	7 (4–10)*
Duration of symptoms until ED presentation, Range	0–32*
Median length of stay (IQR)	6 (3–11)*
Length of stay, Range	1–164*

* : presented in days.

Table 2
Sensitivity, specificity, PPV and NPV for ICU admission and in-hospital mortality

	ICU admission SI ≥ 0.57	In-hospital mortality SI ≥ 0.86
Sensitivity (95% CI)	78,3% (68.4–86.2%)	12.3% (6.9–19.7%)
Specificity (95%CI)	34.2% (29.0–39.7%)	93.6% (90.2–96.1%)
PPV (95%CI)	25.5% (21.2–37.3%)	42.4% (31.6–56.4%)
NPV (95%CI)	84.5% (76.7–87.3%)	73.5% (59.5–82.4%)

For the SI concerning ICU admission, the optimal cut-off point was 0.57 (Table 2). The AUC was 0.56 (95% CI: 0.49–0.62) with a positive LR of 1.19 (1.04–1.36) and negative LR of 0.64 (0.42–0.97). A SI ≥ 0.57 was measured in 282 patients (69%), of which 81 died (29%) and 72 were admitted to the ICU (26%).

4. Discussion

In this cohort of patients hospitalized with COVID-19, SI measured at ED presentation was not discriminative for ICU admission or in-hospital mortality. As such, it was not useful to identify patients at risk for clinical deterioration.

With regards to the optimal cut-off point of 0.57 for ICU admission, sensitivity and specificity were both unsatisfying. This may not be a surprise, because this is a SI in the normal range of 0.5–0.7 [8] and is therefore not discriminative. The optimal cut-off point for in-hospital mortality has a high specificity but low sensitivity. For early identification of patients at risk for adverse outcomes, the ideal test would have a high sensitivity. If so, intensive monitoring could be initiated in patients with an elevated SI. However, this study does not indicate the SI as such a score in patients with COVID-19.

Only few studies examined the presence of shock or hemodynamic instability in COVID-19 patients. A large retrospective study from China observed that 20% of COVID-19 patients in the ICU suffered from shock [12]. Causes for hemodynamic instability included hypovolemia, vasodilation or cardiac dysfunction. The mortality rate in this cohort was over 50%, but cause of death was not reported. Acute respiratory failure was assumed to be the leading cause of death. Although patient demographics in this study were similar to our cohort, the study only assessed ICU patients whilst we assessed all hospitalized patients with COVID-19. Furthermore, the definition of shock was not specified other than by the calculation of the SOFA and APACHE II scores.

Michard and Vieillard-Baron [13] described that several studies reported higher use of vasopressor agents as compared to the Chinese study. Auld et al. [14] observed that 65.9% of ICU patients required vasopressor agents for shock. Patients who died in the ICU were more likely to have received vasopressor agents compared to survivors (90.3% vs 53.7%).

Hu et al. [15] assessed the utility of the Modified Early Warning Score (MEWS) and the Rapid Emergency Medicine Score (REMS), and demonstrated that these scores are suitable to be used as risk stratification tools for in-hospital mortality in COVID-19 patients. The MEWS and REMS include HR, blood pressure (MEWS: SBP; REMS: mean arterial pressure), consciousness level, respiratory rate, oxygen saturation and temperature (MEWS only). Comparing survivors and non-survivors, HR was similar and SBP was significantly higher in the non-survivor group. Similar to our study, hemodynamic parameters were of little value in the early identification of COVID-19 patients at risk of clinical deterioration.

The SI has proven its value to predict in-hospital mortality in patients with sepsis. However, this risk stratification tool was not equally useful in our cohort of hospitalized COVID-19 patients. In COVID-19, respiratory failure is far more common than (and usually preludes) hemodynamic instability, which may explain the limited utility of the SI in COVID-19 patients in the ED who require hospitalization. Furthermore, the hemodynamic problems that ensue in patients admitted to the ICU may be partially explained by the use of anesthetics for invasive mechanical ventilation. Therefore, oxygen saturation, respiratory rate and consciousness levels may be more useful to identify patients at risk for clinical deterioration in the ED than hemodynamic parameters including SI.

The association between SI and mortality is weaker in older patients, patients with hypertension and patients using beta blocking or calcium blocking agents [16]. This may have also weakened the association of the SI with negative outcomes in our study, as the majority of this cohort was 65 years or older, 53% of patients had hypertension and 39% of patients were using beta blocking or calcium blocking agents.

To date, one other study examined the utility of SI in ED patients with COVID-19 [17]. It was observed that a SI above 0.93 showed a significant correlation with mortality rates, especially in older age. Early identification of patients with high risk of mortality was further

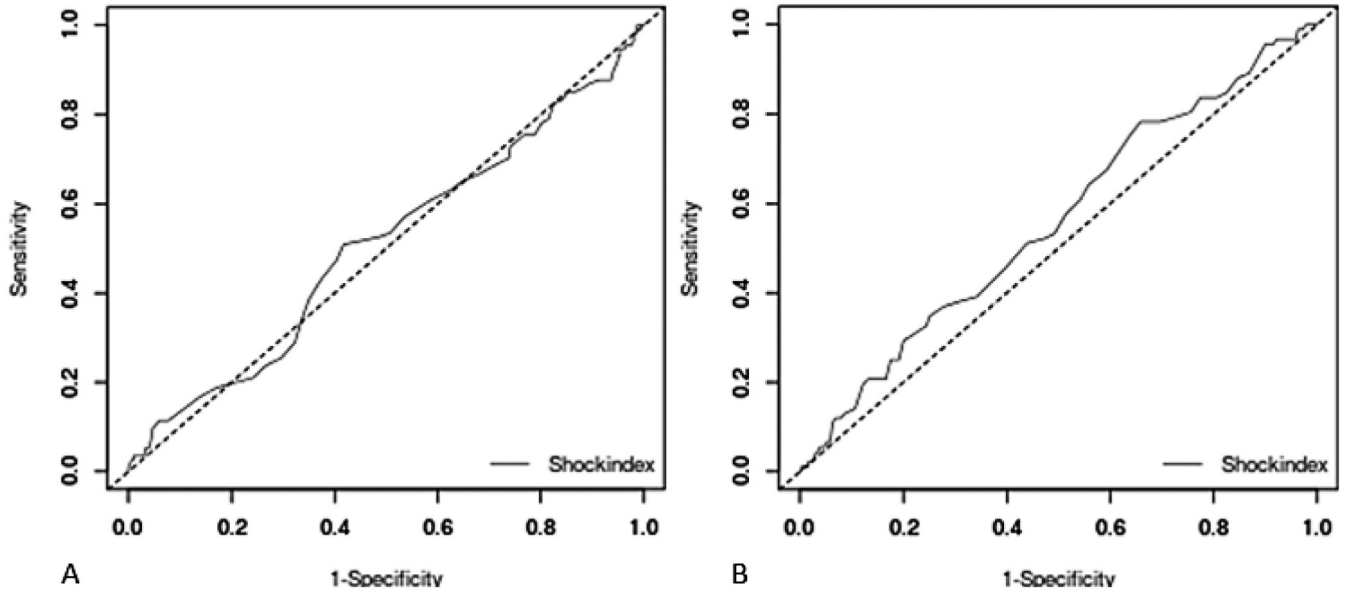

Fig. 1. ROC. A: SI concerning in-hospital mortality, B: SI concerning ICU admission.

improved when the SI was combined with oxygen saturation levels: none of the patients with SpO2 levels above 95% died. The correlation of SI with mortality rates was not replicated in our cohort, which may be explained by several factors. First, the Netherlands is well-known of its well-developed primary care system, which may have caused differences in disease severity between the two cohorts, as well as the time from symptom onset until ED presentation. For example, frail older patients at high risk of in-hospital mortality may have not been referred to the hospital in our cohort. Similarly, younger patients at low risk of clinical deterioration and/or SpO2 > 95% were rarely admitted. Therefore, direct comparison of the two cohorts is complicated, and the contradicting results warrant further prospective studies.

This study has several limitations. First, data were collected retrospectively with potential limitations in accuracy of reporting. Second, this was a single-center study. Third, the SI was only calculated for the ED visit. Monitoring patients by taking consecutive SI measurements could possibly be more helpful for the early detection of clinical deterioration. However, hemodynamic instability probably occurs later in the disease process, when the patients have already sustained major respiratory compromise. Therefore, future studies should assess the utility of consecutive SI measurements in hospitalized patients with COVID-19. Finally, the study sample size is limited to 411 patients, which means that only moderate to large effect sizes could have been shown. Therefore, it seems unlikely that a more comprehensive cohort study with larger sample size would result in clinically relevant utility of the SI (e.g. an LR+ of 5.0 or 6.0) in patients hospitalized with COVID-19.

5. Conclusion

In this cohort of patients hospitalized with COVID-19, SI measured at ED presentation was not discriminative for ICU admission and was not useful for early identification of patients at risk of clinical deterioration.

Declaration of Competing Interest

The authors have no relevant financial information or potential conflicts of interest to disclose.

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