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Original article

Intensive Care Infection Score (ICIS) is elevated in patients with moderate and severe COVID-19 in the early stages of disease

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus is still a very dangerous and life-threatening disease with an extremely heterogeneous course. Older patients and those with co-morbidities are at increased risk of death from the disease but young patients can develop potentially lethal complications too. For those reasons, numerous recent studies focus on the analysis of markers associated with early assessment of COVID-19 prognosis. Previous publications provided evidence for the Intensive Care Infection Score (ICIS) as an easy to use tool to assess the risk for bacterial infection in ICU patients based on a combination of haematologic parameters. This study evaluated the performance of ICIS as a prognostic marker of stages of disease in COVID-19 patients.

Methods: A total of 205 COVID-19 patients admitted to the University Hospital Hradec Kralove, Czech Republic, with symptoms of respiratory tract infection and a positive RT-PCR test for SARS-CoV-2 virus were enrolled in this study. Forty-nine patients developed mild COVID-19 symptoms (no oxygen therapy needed), 156 patients developed moderate or severe symptoms (supplemental oxygen therapy or death).

Results: ICIS predicted the mild or moderate/severe course with the highest AUC (0.773). The cut-off value (ICIS = 3.5) was selected as the value with the highest Youden index (0.423). The cut-off value could predict a mild or moderate/severe course of the disease with the highest specificity (77.6%) and positive predictive value (90.2%) of all markers used in this study. Sensitivity was 64.7%.

Conclusion: ICIS is a reliable, cheap, fast and simply interpretable score for the early identification of moderate/severe course of COVID-19 in an early stage of the disease. ICIS > 3 predicts a severe course of the disease with high specificity and positive predictive value.

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Introduction

Despite all the efforts, Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus is still a very dangerous and life-threatening disease in many cases. The clinical course of COVID-19 is extremely heterogeneous. Some patients develop moderate/severe pneumonia, acute respiratory distress syndrome, multiple organ failure and can succumb to the disease while others develop asymptomatic COVID-19 and don't show any key COVID-19 symptoms during the disease [1–3]. Older patients and those with co-morbidities are at increased risk of death from the disease but young patients can develop potentially lethal complications too. Many patients with moderate/severe COVID-19 require oxygen support and must thus be admitted to a hospital and need much more at-

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tention [4]. For those reasons, numerous recent studies specialise in the analysis of markers associated with early assessment of COVID-19 prognosis [5–7]. Patients with unfavourable prognostic features could be admitted to a hospital providing a higher quality of care (including oxygen supply), optimally managed and have an increased probability of survival or at least a less complicated course of the disease.

Recent studies identified many laboratory abnormalities related to COVID-19 viral infection. White blood cell count can be decreased. COVID-19 related pneumonia can lead to neutrophilia, lymphopenia and an increased neutrophils/lymphocytes ratio (NLR) [8,9]. Thrombocytopenia, anaemia of chronic disease and decreased haemoglobin concentration in reticulocytes can also be present [10]. D-dimers, fibrinogen, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCT), interleukin-6 (IL-6), ferritin or some cardio markers can be elevated too [6,11]. Aberrant concentrations of the markers can be different between cohorts of patients with different clinical outcomes and some of them can be used as relevant prognostic markers [12,13].

The aim of this study is to evaluate the use of the Intensive Care Infection Score (ICIS), for the early identification of severe course COVID-19 patients. ICIS is research use only tool developed by the company Sysmex Europe (Hamburg, Germany). In short, ICIS score (0–20) correlates well with the likelihood for bacterial infection in Intensive Care Unit (ICU) patients and there is published evidence to being used as an aid in the diagnosis and management of septic patients [14–16]. It is calculated from the complete blood count, differential count of leukocytes and reticulocyte count values (mean fluorescence intensity of mature neutrophils, the difference in haemoglobin concentration between reticulocytes and mature red blood cells, total segmented neutrophil count, antibody-synthesising lymphocyte count and immature granulocyte count) [14]. It can reflect early responses of the immune system to infection and could be a candidate prognostic marker stratifying COVID-19 patients to clinically relevant groups at the time of diagnosis.

Patients and methods

Study design

Patients (age ≥ 16 years) with a confirmed diagnosis of COVID-19 admitted to the University Hospital Hradec Kralove, Czech Republic, between 1st Oct 2020 and 23rd Nov 2020 were enrolled in this study. Patients with previously diagnosed haematological malignancies were omitted due to exhibiting haematopoietic dysplasia which interferes with a proper ICIS score assessment. Patients with COVID-19 infection were divided into two groups: The first group contained patients with mild symptoms with oxygen saturation greater than 92%, who did not require any supplemental oxygen therapy during the disease. The second group contained patients with moderate/severe symptoms, who required supplemental oxygen therapy, high-flow nasal oxygen therapy or artificial pulmonary ventilation or succumbed to the disease. The study was conducted according to the Helsinki Declaration, approved by the local ethics committee and all study participants provided written informed consent.

Blood analysis

Blood samples for complete blood count and ICIS assessment were taken on time of admission to the hospital or on day of COVID-19 diagnosis (already hospitalized patients). Samples of 78 patients (38%) were taken on day of positive PCR test for COVID-19 but it differed in others because the complete blood count and ICIS were assessed when they came to the hospital due to the worsening of their previously diagnosed COVID-19 disease. All laboratory parameters (complete blood count, differential count, reticulocytes) were measured on a fully automated Sysmex XN-3000 analyser (Sysmex, Kobe, Japan) according to the manufacturer's instructions and ICIS score was calculated as described by Nierhaus A et al. [14].

Statistical analysis

Statistical analysis was performed using a free software environment for statistical computing and graphics R [17] version 4.0.2. pROC package [18] was used for the receiver operating characteristic (ROC) curve analysis. Areas under ROC curves (AUC) > 0.70 were considered clinically relevant [19]. The best cut-off values were determined as values with the highest Youden index (best combined sensitivity and specificity using ROC-curve analysis). The association between quantitative traits was evaluated by a two-tailed Mann-Whitney U test as all data were non-normally distributed. The association of qualitative traits was evaluated by Fisher exact test. P-values lower than 0.05 were considered statistically significant.

Results

Cohort characteristics

A total of 205 patients admitted to the University Hospital Hradec Kralove, Czech Republic, with symptoms of respiratory tract infection and positive RT-PCR test for SARS-CoV-2 virus from a nasal swab diagnosed between 1st Oct 2020 and 23rd Nov 2020 were enrolled in this study. The patients were not stratified according to their age but most of them were adults (> =18 years old). Only one patient was younger (16) but she was admitted to the adult ward and thus included in the study. There were 126 males and 79 females with a median age of 69 (16–98) years. 49 patients developed mild COVID-19 symptoms (no oxygen therapy needed) and 156 patients developed moderate or severe symptoms (oxygen-dependent patients and those who succumbed to the disease) (see Table 1 for a summary). 99 patients of the former cohort received oxygen therapy, 14 high-flow nasal oxygen therapy, 8 non-invasive pressure ventilation,

Table 1
Patient characteristics: ICIS (Intensive Care Infection Score).

	Mild COVID-19	Moderate/Severe COVID-19
Age median (range)	53 (26–89) years	73 (16–98) years
Sex Female / Male	21 / 28	58 / 98
Course of COVID-19	49	156
ICIS Low / High	38 / 11	55 / 101

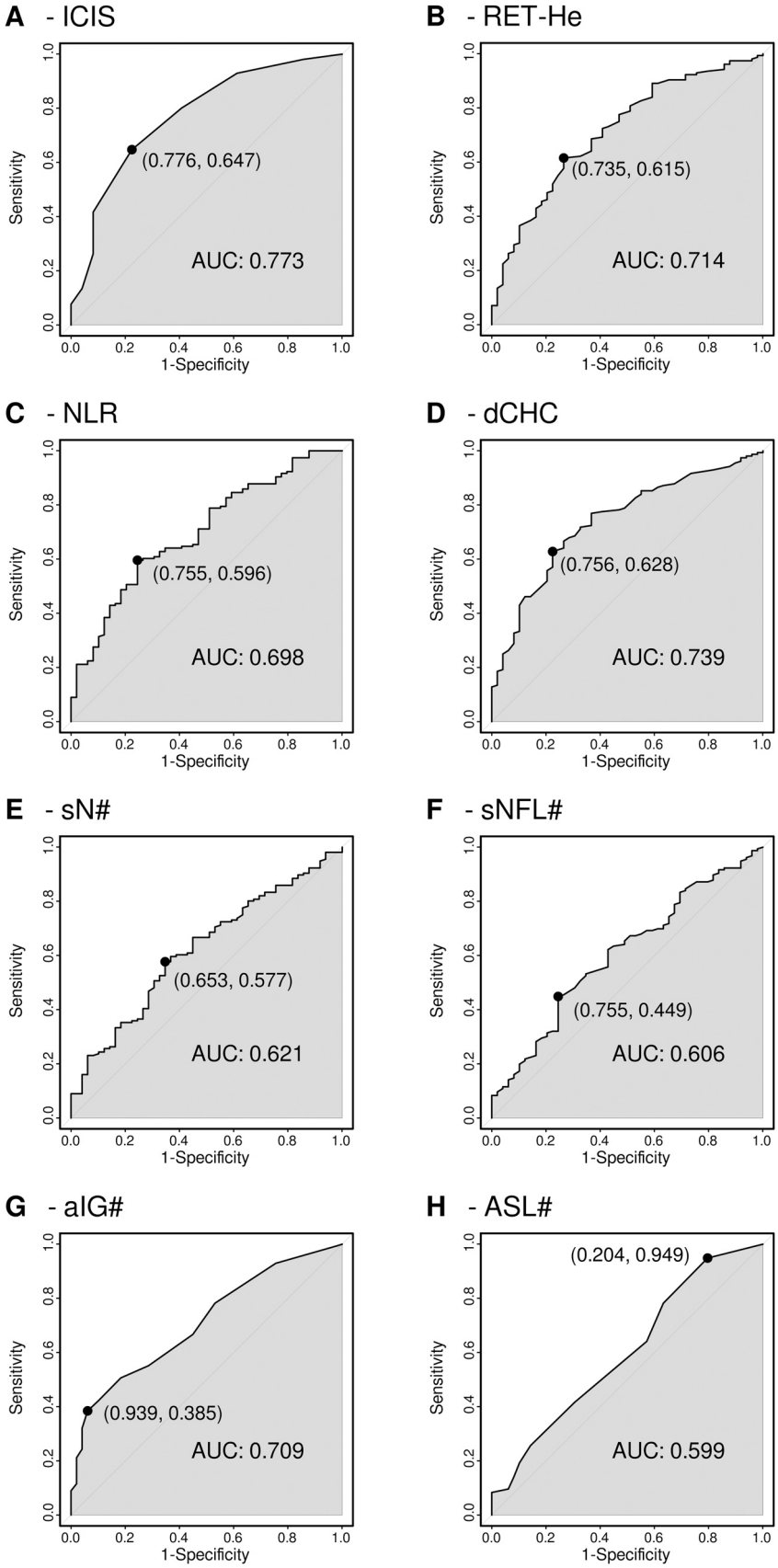

Fig. 1. Predictive values of selected markers for severe course of COVID-19. Predictive value was computed using receiver operator characteristic (ROC) curves and area under curve (AUC). Thresholds with the highest Youden index are marked with a circle (with specificity and sensitivity in parentheses). A: Intensive Care Infection Score (ICIS), B: reticulocyte haemoglobin equivalent (RET-He), C: Neutrophils to lymphocytes ratio (NLR), D: difference in haemoglobin concentration between newly formed and mature red blood cells (dCHC), E: absolute segmented neutrophils count (sN#), F: mean fluorescence intensity of mature neutrophils (sNFL#), G: accurate immature granulocytes count (aIG#) and H: antibody synthesising lymphocytes (ASL#).

Table 2
Parameters used for differentiating mild from severe COVID-19: ICIS: intensive care infection score, NLR: neutrophils to lymphocytes ratio, dCHC: difference in haemoglobin concentration between newly formed and mature red blood cells, RET-He: reticulocyte haemoglobin equivalent, sN#: absolute segmented neutrophils count, sNFL#: mean fluorescence intensity of mature neutrophils, aIG#: accurate immature granulocytes count, ASL#: absolute count of antibody synthesising lymphocytes.

	AUC	Best threshold	Youden index	Sensitivity	Specificity
ICIS	0.773	3.500	0.4229	0.6474	0.7755
NLR	0.698	4.370	0.3513	0.5962	0.7551
dCHC	0.739	0.150	0.4037	0.6282	0.7755
RET-He	0.714	31.950	0.3501	0.6154	0.7347
sN#	0.621	4.630	0.2300	0.5769	0.6531
sNFL#	0.606	52.25	0.2038	0.4487	0.7551
aIG#	0.709	0.075	0.3234	0.3846	0.9388
ASL#	0.599	0.005	0.1528	0.9487	0.2041

18 artificial pulmonary ventilation and 17 succumbed without any oxygen supplement. Other therapy management was performed based on Centers for Disease Control and Prevention (CDC) [20] and local guidance.

Differences in demographic and haematological parameters

The demographic and relevant haematological parameters on admission were compared between patients with mild and moderate/severe disease. We selected haematological markers used to calculate ICIS to assess if any of them is better in the classification of COVID-19 patients than ICIS. There was no statistically significant difference in gender between the two groups but they differed in age ($p < 0.001$) with a higher median age in the group of patients with moderate/severe COVID-19. The groups didn't differ in the count of white blood cells ($p = 0.123$). Haemoglobin concentration ($p < 0.001$), total lymphocyte count ($p < 0.001$) and reticulocyte haemoglobin equivalent ($p < 0.001$) were significantly lower in the group with moderate/severe COVID-19. Neutrophil-to-lymphocyte ratio (NLR) ($p < 0.001$), difference in haemoglobin concentration between reticulocytes and mature red blood cells (dCHC) ($p < 0.001$), absolute segmented neutrophils count (sN#) ($p = 0.011$), mean fluorescence intensity of mature (sNFL#) ($p = 0.023$), accurate immature granulocytes count (aIG#) ($p < 0.001$) and antibody synthesising lymphocytes (ASL#) ($p = 0.030$) were significantly higher in the group with moderate/severe COVID-19.

Stratifying patients according to risk

A ROC curve was used to evaluate how well each of the parameters sorts patients into groups according to the oncoming course of the disease (see Fig. 1). The best model used ICIS as a predictor with AUC = 0.773, indicating the good diagnostic value of the parameter. Maximum Youden index 0.443 (sensitivity 64.7%, specificity 77.6%) was reached when the threshold was set to value 3.5. The positive predictive value in our cohort was 0.902. Results for all tests are summarised in Table 2. Patients with ICIS < 3.5 had a significantly better outcome than patients with ICIS > 3.5 ($p < 0.001$). The positive predictive value of ICIS for a moderate/severe course of COVID-19 in our cohort of patients was 90.2%.

Discussion

Since the first study in China describing the disease [21], COVID-19 has spread all over the world and it was declared a pandemic by the World Health Organization (WHO) on 11th February 2020 [22]. Despite all the efforts, COVID-19 is still a very dangerous and life-threatening disease with heterogeneous clinical course and early identification of patients with moderate/severe clinical course remains a challenge. There are studies showing biochemical and haematological markers that can be used to identify patients with moderate/severe COVID-19 in the early stages of the disease [5–7]. The aim of this study was to evaluate the prognostic value of ICIS in a cohort of 205 COVID-19 patients admitted to University Hospital in Hradec Kralove, Czech Republic. ICIS aggregates results of five parameters measured by haematology analysers [15]. The parameters reflect the innate immune response right from the initial exposure up to the infection course days later and all parameters reflect the phase and severity of infection. ICIS was developed with primary aim to add information for judging the condition of the patient and for taking treatment decisions in the cohort of septic ICU patients primarily caused by bacteria [14–16]. For specific viral SARS-CoV-2 outbreak and related challenges of differentiating between mild or moderate/severe cases of COVID-19 disease course of infection early on, a new tailor-made prognostic score has been recently developed and validated in a large multicentric study. This prognostic score showed ROC curve AUC at baseline of 0.753 increasing to 0.875 on day 3 after admission. The COVID-19 prognostic score is composed of several additional parameters such as RE-MONO# (reactive monocytes count) or NRBC#, but also contains three parameters (IG#, AS-LYMPH# and Delta-He) closely related to the ones that are part of the ICIS score evaluated in this study. Similarly as ICIS in our study, the COVID-19 prognostic score was superior to any individual parameter as well as NLR at distinguishing between clinical severity [23].

We have demonstrated that ICIS discriminates patients with moderate/severe course of COVID-19 with high specificity (77.6%) and positive predictive value (90.2%). The AUC and maximum Youden index of ICIS were superior to the parameters ICIS is comprised of and it can be used as a prognostic marker for COVID-19. Using ICIS has several advantages over established prognostic markers such as D-dimers, PCT or IL-6. No extra blood is needed when a complete blood count is analysed since ICIS can be measured from K_3EDTA anticoagulated blood by a fully automated

blood analyser within 60 s without the need for sample preparation. It is very cost-effective because only CBC, differential count and reticulocytes (all measured simultaneously) are needed to calculate ICIS. ICIS represents a new, accessible and valid marker for discriminating patients in the early phases of COVID-19. Using a cut-off value of 3.5 (> 3) was the best threshold in our cohort of patients, which is in concordance with or similar to some studies using ICIS as an early marker of infection or sepsis [14,15].

Some limitations of our study must be considered. The composition of the cohort may be biased since our hospital is a specialised medical facility. But the high positive predictive value of ICIS seems to be promising and such results should apply to other facilities with different moderate/severe to mild COVID-19 ratios. Patients with a previously diagnosed haematological malignancy were omitted due to hematopoietic dysplasia. The prognostic value of ICIS in this cohort could be analysed too regardless of the limitation previously mentioned.

Conclusions

In conclusion, the present study demonstrates that ICIS, a cheap, fast and simply interpretable currently research use only score measured by Sysmex XN analysers, can be used to support the identification of patients with a moderate/severe course of COVID-19 in the early stages of the disease. Further studies with combinations of ICIS and other markers could be very interesting and they could lead to more accurate prognostic markers than currently available.

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Conflict of interest

All authors have no conflict of interest to declare.

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All authors read and approved the final manuscript. Filip Vrbacky: analysed and interpreted the patient data and was a major contributor in writing the manuscript. Ilona Fatorova: analysed and interpreted the laboratory data. Martin Blazek: analysed and interpreted the clinical data. Petr Smahel: analysed and interpreted the clinical data. Pavel Zak: analysed and interpreted the clinical data, was a contributor in writing the manuscript and senior author. The ICIS was kindly provided by Sysmex Czech for research purposes.

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