Reassessment of disease severity routine laboratory tests in the COVID-19 infection

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Introduction. Publications demonstrate some limitations of National Early Warning Score 2 (NEWS-2) accuracy in assessment on coronavirus infection severity. The purpose of this study was to determine the value of the patient’s age and routine laboratory parameters in the assessment of patient’s general condition in coronavirus pneumonia and their relation to NEWS-2 scale parameters.

Materials and methods. 50 case reports of patients with COVID-19 infection observed in the Sechenov University in January–March 2021 were analyzed. 34 % of patients were males aged 31 to 89 years (average age 55 years) and 66 % — females aged 40 to 91 (mean age 63). The diagnosis of pneumonia was confirmed by computed tomography. NEWS-2 scale total score was assessed.

Results. According to the physician’s subjective assessment the condition was significantly more often assessed as moderate and severe. There was only a weak correlation between the blood oxygen saturation and the total NEWS-2 score ($r = 0.165, \alpha = 0.1$). We found a mild correlation ($r = 0.341, \alpha = 0.1$) between the patient’s age and NEWS-2 score. Among the most significantly interrelated parameters were age, neutrophil count, serum creatinine, CRP, fibrinogen level. Seven interrelated parameters (age, body temperature, blood oxygen saturation, the neutrophils count, creatinine, CRP, fibrinogen), for which a reliable relation with other tests has been shown, were assigned with its special index according to their contribution to the assessment of the overall condition severity. An aggregated score (criterion X) was proposed for assessment of disease severity according to equation. The proportions of mild, moderate, and severe cases according to criterion X were 12 %, 64 % and 24 %.

Conclusion. The preliminary results obtained in the study emphasize the importance of routine laboratory tests in assessment of coronavirus infection severity. An evident discrepancy between NEWS-2 score and X criterion may be very important for practice.

Keywords: COVID-19 infection, NEWS-2 scale, routine laboratory tests

Conflict of interest: the authors declare no conflict of interest.


Пересмотр значения рутинных лабораторных параметров в оценке тяжести течения инфекции COVID-19

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Цель. Из литературы известны определенные ограничения точности протокола оценки тяжести состояния пациента (National Early Warning Score 2 (NEWS-2)) в оценке тяжести коронавирусной инфекции. Целью данного исследования было определить значение возраста пациента и рутинных лабораторных параметров в оценке общего состояния пациента при коронавирусной пневмонии и их связь с параметрами шкалы NEWS-2.

Материалы и методы. Проанализировано 50 историй болезни пациентов с инфекцией COVID-19, наблюдавшихся в Сеченовском Университете в январе — марте 2021 г. Из них 34 % пациентов составили мужчины в возрасте от 31 до 89 лет (средний возраст 55 лет), и 66 % — женщины в возрасте от 40 до 91 года (средний возраст 63 года). Диагноз пневмонии был подтвержден с помощью компьютерной томографии. Оценивался общий балл по шкале NEWS-2.
**Introduction**

Medical prognostic scales are widely used in everyday practice providing an optimal assessment of disease severity and prognosis [1, 2]. As examples, APACHE III and SAPS II integrating a number of important homeostatic parameters (body temperature, blood pressure, oxygen blood saturation, etc.) are traditionally used as universal scales in acute and chronic illnesses [1, 2].

The National Early Warning Score 2 (NEWS-2) protocol has been introduced not so long ago for dynamic assessment of the patient condition to define the need in additional investigations and transferring to the intensive care unit. This scale comprises 8 most important clinical parameters: body temperature, systolic blood pressure, heart rate and respiratory movements per minute, oxygen saturation according to pulse oximetry data, the need for oxygen support, and the changes in consciousness (Table 1) [3].

In low total NEWS-2 score (1–4) clinicians need to decide if closer monitoring or escalation of care is needed. In median score (5–6) or any single score of 3 an urgent review by skilled medical personnel is strictly recommended. And in a high score (≥7) emergency assessment by a clinical team/critical care team should be done [3].

The NEWS-2 scale seems to be a simple and convenient screening tool, especially valuable at the stage of patient’s triage in conditions of high workload of the doctor.

Total NEWS-2 score ≥5 predicts a severe complication in the nearest future with a sensitivity of 0.98 (95% CI 0.96–1.00) and a specificity of 0.28 (0.21–0.35). The positive predictive value of NEWS-2 total score ≥5 has is 0.53 (0.47–0.59), while the negative predictive value is so high as 0.96 (0.90–1.00). Hence, the negative predictive value of NEWS-2 score ≥5 is the most valuable feature of this scale in clinical practice [3].

NEWS-2 was proposed for assessment of COVID-19 infection severity. The fact of COVID-19 infection is not included with the total score, but it is reasonable to indicate it on a separate line for the scientific purpose [4]. Publications concerning the experience of NEWS-2 application in coronavirus infection have demonstrated some limitations of its accuracy. In fact, the severity of the patient’s condition and the effectiveness of treatment are not strictly interrelated with the acute pathophysiological abnormalities recorded by NEWS-2 [4–7]. Probably, individual adaptive response depending on age, duration of the infection before admission, concomitant diseases and medications can affect the informative value of NEWS-2. Critical analysis by English researchers underlines such a shortcoming as an assessment of the oxygen demand as “yes” or “no” answer [6]. The authors emphasize the risk of dramatic complications in patients with progressing hypoxia if medical personnel is not adequately educated in this problem. The paper proposes a special algorithm for oxygen demand assessment [6].

Another article discusses the scenarios of coronavirus pneumonia emphasizing their “impressive uniformity” — from “silent” hypoxemia to severe shortness of breath [7]. The significant fluctuations in blood carbon dioxide may be explained in particular by the disturbed tissue vascular regulatory response. The concomitant diseases and the time elapsed from the COVID-19-infection onset may also play a significant role [7]. Great variability in “physiological reserve” in coronavirus infection substantiates reassessment of NEWS-2 accuracy and the value of other routine parameters [5].

The purpose of this study was to determine the value of the patient’s age and routine laboratory parameters in the assessment of patient’s general condition in coronavirus pneumonia and their relation to NEWS-2 scale parameters.
Table 1. The NEWS-2 scale
Таблица 1. Оценка по шкале NEWS-2

<table>
<thead>
<tr>
<th>Physiological parameter</th>
<th>Score</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate (per min)</td>
<td>≤8</td>
<td>9–11</td>
<td>12–20</td>
<td>21–24</td>
<td>≥25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sat O₂, %</td>
<td>≤91</td>
<td>92–93</td>
<td>94–95</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxygen support</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>≤90</td>
<td>91–100</td>
<td>101–110</td>
<td>111–219</td>
<td>≥220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate (per min)</td>
<td>≤40</td>
<td>41–50</td>
<td>51–90</td>
<td>91–110</td>
<td>111–130</td>
<td>≥131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consciousness</td>
<td>Alert</td>
<td>CVPU (confusion, voice, pain, unresponsive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>≤35,0</td>
<td>35,1–36,0</td>
<td>36,1–38,0</td>
<td>38,1–39,0</td>
<td>≥39,1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Materials and methods

50 case reports of patients with COVID-19 infection observed at the University Clinical Hospital N 2 of the Sechenov University in January–March 2021 were analyzed. 17 (34 %) of patients were males aged 31 to 89 years (average age 55 years) and 33 (66 %) females aged 40 to 91 (mean age 63).

All the patients were examined according to the medical insurance standards recommended by the Ministry of Health of the Russian Federation for COVID-19 infection and coronavirus pneumonia. Recommended laboratory tests were performed with the 3–5 days intervals. The diagnosis of pneumonia was confirmed by computed tomography, and COVID-19 infection was confirmed by PCR in a throat swab. At the time of admission and during the observation, the NEWS-2 scale total score was assessed.

49 patients were diagnosed with COVID-19 infection with polysegmental pneumonia of variable severity (41 — bilateral and 8 — unilateral pneumonia). In 1 case of bilateral pneumonia, COVID-19 infection was not confirmed by PCR results. Among the concomitant diseases were coronary disease (n = 11, 22 %), arterial hypertension (n = 21, 42 %), arhythmia (n = 6, 12 %), dyscirculatory encephalopathy (n = 2, 4 %), aortic aneurism (n = 2, 4 %), Clostridium difficile-infection (n = 5, 10 %), diabetes mellitus 2 type (n = 4, 8 %), malignancy (n = 3, 6 %), obesity (n = 14, 28 %), chronic bronchitis (n = 1, 2 %), hypothyroidism (n = 2, 4 %), uncomplicated gallstone disease (n = 4, 8 %), uncomplicated urolithiasis (n = 4, 8 %), peptic ulcer (n = 9, 18 %), iron-deficient anemia (n = 1, 2 %).

Figure 1 shows the patients distribution by the disease severity at the time of admission according to the subjective physician (routine) assessment based on traditional clinical parameters (body temperature, state of consciousness, severity of intoxication, degree of lung injury, respiratory rate, heart rate) and laboratory data, as well as according to the NEWS-2 scale. The figure demonstrates that these two approaches (the subjective assessment and NEWS-2 score) may give different results. According to the physician’s subjective assessment, the condition was significantly more often assessed as moderate and severe, while the NEWS-2 scale showed a higher proportion of mild cases.

To clarify the mechanism of such a discrepancy, a correlation analysis of some NEWS-2 parameters (heart rate, patient’s body temperature, blood oxygen saturation according to pulse oximetry) and also patient’s age with total NEWS-2 score was carried out. The table 2 represents the most important results. Although heart rate and body temperature are the important components of NEWS-2 total score, they apparently are not closely related to the total
result. There was only a weak correlation between the blood oxygen saturation and the total NEWS-2 score (correlation coefficient \( r = 0.165, \alpha = 0.1 \)). We found a mild correlation (\( r = 0.341, \alpha = 0.1 \)) between the patient’s age and the total NEWS-2 score, although age is not included into the scale.

It is well known the severity of inflammation and damage is also characterized by laboratory tests: white blood cell count and formula, erythrocyte sedimentation rate, serum concentration of C-reactive protein (CRP), fibrinogen, potassium, sodium, alanine (ALT) and aspartic (AST) transaminases, glucose. These parameters are available for any medical institution and are easily reproducible. In this study, we didn’t find any significant correlation of these tests with total NEWS-2 scale excepting neutrophil count (\( r = 0.186, p < 0.05 \)).

Because of laboratory deviations usually should be assessed as an integral system, correlation analysis was carried out between different tests, before the beginning of anti-inflammatory therapy.

Among the most significantly interrelated parameters were patient’s age, neutrophil count, serum creatinine, CRP and fibrinogen level (Table 3). These parameters are routinely used for assessment of

**Table 2.** The results of the correlation analysis between the total NEWS-2 score and some important clinical parameters

<table>
<thead>
<tr>
<th>Parameter for correlation analysis with total NEWS-2 score</th>
<th>Correlation coefficient, ( r )</th>
<th>Correlation significance, ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate ( \text{Частота сердечных сокращений} )</td>
<td>0.057</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Body temperature ( \text{Температура тела} )</td>
<td>0.040</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Blood oxygen saturation ( \text{Насыщение крови кислородом} )</td>
<td>-0.167</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patient age ( \text{Возраст пациента} )</td>
<td>0.341</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Table 3.** The results of correlation analysis of laboratory parameters

<table>
<thead>
<tr>
<th>Parameters for correlation analysis</th>
<th>Correlation coefficient, ( r )</th>
<th>Correlation significance, ( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils count and serum CRP level ( \text{Число нейтрофилов и уровень сывороточного C-реактивного белка} )</td>
<td>0.347</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Patient age and serum creatinine level ( \text{Возраст пациента и уровень сывороточного креатинина} )</td>
<td>0.258</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>White blood cell count and serum fibrinogen level ( \text{Число лейкоцитов и уровень сывороточного фибриногена} )</td>
<td>0.415</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Neutrophils count and serum fibrinogen level ( \text{Число нейтрофилов и уровень сывороточного фибриногена} )</td>
<td>0.599</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Fig. 1. Patient’s distribution by the disease severity according to generally accepted clinical criteria and according to the NEWS-2 scale

Рис. 1. Распределение пациентов по тяжести заболевания в соответствии с общепринятыми клиническими критериями и по шкале NEWS-2
Table 4. The indices (“relative weight”) of estimated laboratory parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age (A)</th>
<th>Body temperature (T)</th>
<th>SatO₂ (S)</th>
<th>Neutrophil count (N)</th>
<th>Creatinine (Cr)</th>
<th>CRP (C)</th>
<th>Fibrinogen (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation with NEWS-2 (r)</td>
<td>0.34</td>
<td>0.04</td>
<td>-0.17</td>
<td>0.186</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Correlation with X (r)</td>
<td>0.37</td>
<td>0.23</td>
<td>-0.37</td>
<td>0.42</td>
<td>0.31</td>
<td>0.96</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Based on represented indices, an aggregated score (criterion X) was proposed for assessment of disease severity:

\[
X = 0.01 \cdot (16A + 6T + 8S + 13N + 16Cr + 26C + 15F).
\]

Comment: X is the number of calculated points characterizing the severity of the patient’s condition; coefficient 0.01 was introduced to reduce the rank (the total sum of estimated indices is accepted to be 100); the values of indices and the names of estimated parameters are represented in brackets (A — age, T — body temperature, S — blood oxygen saturation, N — neutrophils, Cr — creatinine, C — CRP, F — fibrinogen).

In the studied group of patients X criterion ranged from 36 to 106. Matching X criterion for each case according to the physician’s subjective assessment of the disease severity, the following intervals were found: X criterion score ≤40 indicates a mild form of the disease; 41 ≤ X ≤ 63 indicates a moderate severity; X > 63 — a severe form of the disease. According to this, the severity of 50 cases analysed in the study might be assessed as mild in 6 (12 %), moderately severe in 32 (64 %), and severe in 12 (24 %) cases (Fig. 2).

Discussion

Any of prognostic scale helps to assess the patient’s condition only with some approximation. In this study we noted the significant discrepancies in COVID-19 infection severity assessment according to subjective physician assessment and according to NEWS-2 scale (Fig. 2). This fact seems to be the most important in cases of coronavirus pneumonia which is characterized by highly dynamic pathophysiological changes with impaired vascular response especially in patients in advanced age, having concomitant pathologies and longer duration of disease. Other authors also underline the insufficient reliability of NEWS-2 scale for nearest prognosis in COVID-19 infection [4–7].

The proportions of mild, moderate, and severe cases according to NEWS-2 were 56 %, 30 % and...
14 %, respectively, versus 12 %, 64 % and 24 % according to criterion X (Fig. 2). Thus, it may be concluded NEWS-2 in some degree may ‘underestimate’ the severity of coronavirus pneumonia. At the same time, this fact may not be so critical as far as the negative predictive value is most valuable in NEWS-2. The absence of reliable relationship between classical serum inflammatory parameters and NEWS-2 score in our study may be explained by the limited group size and wide reference range of some NEWS-2 constituents in (e.g., heart rate, blood oxygen saturation).

The critical assessment of NEWS-2 in coronavirus pneumonia moved us to match the relative significance of routine inflammatory parameters which are traditionally used for assessment of severity of acute illnesses. Laboratory parameters are objective, sensitive, easily reproducible, and accessible to most medical institutions. The close interrelations of different test help to characterize them as an integral system that may be considered as a great advantage of such approach.

We tried to combine by equation seven clinical and laboratory parameters showing the closest interrelation in the investigated group. One of the most significant parameters was the patient’s age which demonstrated the highest correlation with NEWS-2 score and also some lab tests (in particularly, creatinine level). Patient’s age is not included in NEWS-2 although this parameter seems to be very important from the point of view of low physiological reserves. Other parameters in our equation are body temperature, blood oxygen saturation, the neutrophils count, creatinine, CRP, fibrinogen. The criterion X correlates well enough with the values of parameters estimated in it (Table 4). The most significant correlations are shown for neutrophils (moderate strength), fibrinogen (mild correlation) and CRP (very close correlation). Apparently, criterion X is not applicable to patients with leuko- and neutropenia, and there were no such cases in our sample.

The results of disease severity assessment demonstrates that criterion X provides some sort of “average grade” between NEWS-2 score and subjective grade routinely given by physicians (Fig. 2).

Obviously, there may be a need in more profound assessment of the patient’s condition especially in unclear cases. In a cohort study in UK a baseline model of “NEWS-2 + age” was proposed to improve the accuracy of severity of disease assessment. This model had poor-to-moderate discrimination for severe COVID-19 infection at 14 days. The authors raise the question about the introduction of supplemented model adding eight routinely collected blood and physiological parameters (supplemental oxygen flow rate, urea, age, oxygen saturation, C-reactive protein, estimated glomerular filtration rate, neutrophil count, neutrophil/lymphocyte ratio) as a screening tool at hospital admission [5].

The preliminary results obtained in our small-sized study also emphasize the importance of laboratory parameters in assessment of coronavirus infection severity. An evident discrepancy between NEWS-2 score and criterion X may be very important for practice. Probably it is due to relative stability of serum parameters in contrast to vital parameters which may be influenced by a large number of labile factors.

In conclusion it may be reasonable to study X criterion more precisely in large cohorts of patients with COVID-19 infection.

References / Литература
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