Prediction of mortality, requirement of ICU and hospitalization: the COVID-outcome prognostic score

Eduardo Nieto-Ortega  
Sociedad Española de Beneficencia

Alejandro Maldonado Arenal  
Sociedad Española de Beneficencia

Lupita Escudero-Roque  
Sociedad Española de Beneficencia

Diana Ali Macedo-Falcon  
Sociedad Española de Beneficencia

Ana Elena Escorcia-Saucedo  
Sociedad Española de Beneficencia

Adalberto León Ángel  
Sociedad Española de Beneficencia

Alejandro Durán Méndez  
Sociedad Española de Beneficencia

Karla García-Callejas  
Sociedad Española de Beneficencia

Sergio Hemández-Islas  
Sociedad Española de Beneficencia

Gabriel Romero-López  
Sociedad Española de Beneficencia

Ángel Raúl Hernández-Romero  
Universidad Autónoma del Estado de Hidalgo

Daniela Pérez-Ortega  
Sociedad Española de Beneficencia

Estephany Rodríguez-Segura  
Sociedad Española de Beneficencia

Daniela Montaño-Olmos  
Sociedad Española de Beneficencia

Jeffrey Hemández-Muñoz  
Sociedad Española de Beneficencia

Samuel Rodríguez-Peña
Article

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Abstract

Prognostic scales may help to optimize the use of hospital resources, which may be of prime interest in the context of a fast spreading pandemics. Nonetheless, such tools are underdeveloped in the context of COVID-19. In the present article we asked whether accurate prognostic scales could be developed to optimize the use of hospital resources. We retrospectively studied 467 files of hospitalized patients after COVID-19. The odds ratios for 16 different biomarkers were calculated, and those that were significantly associated were screened by a Pearson’s correlation, and such index was used to establish the mathematical function for each marker. The scales to predict the need for hospitalization, intensive-care requirement and mortality had enhanced sensitivities (0.91 CI 0.87–0.94; 0.96 CI 0.94–0.98; 0.96 CI 0.94–0.98; all with $p < 0.0001$) and specificities (0.74 CI 0.62–0.83; 0.92 CI 0.87–0.96 & 0.91 CI 0.86–0.94; all with $p < 0.0001$). Interestingly, when a different population was assayed, these parameters did not change considerably. These results show a novel approach to establish the mathematical function of a marker in the development of highly sensitive prognostic tools, which in this case, may aid in the optimization of hospital resources. An online version of the three algorithms can be found at: http://benepachuca.no-ip.org/covid/index.php

1. Introduction

Two years and ten months after the SARS-CoV-2 pandemics started, more than 621 million cases and more than 6.54 million COVID-19-related deaths have been documented by the World Health Organization (WHO) [1]. In such a rapid growing outbreak hospital resiliency has been repeatedly challenged worldwide [2], imposing an important toll on the physical and mental health of healthcare workers [3, 4], and leading to the saturation of regular hospital beds and intensive care unit (ICU) beds, thus producing a reduction on the quality of medical attention [5], which may have impacted in an enhanced mortality, not only in SARS-CoV-2 patients, but on the totality of cases.

Moreover, in some developing countries healthcare centers reached a complete saturation by COVID-19 patients, leaving many SARS-CoV-2 positive and negative patients without a hospital bed [6, 7]. Arguably, many of the coronavirus-related hospitalizations were unnecessary, and those patients could have been treated at home, freeing hospital resources for patients with enhanced needs. Nonetheless, a precise system to discriminate such cases in order to optimize hospital resource use is lacking.

On the other hand, while more than 80% of COVID-19 patients have a mild to asymptomatic disease, 20% of the patients present moderate to critical forms of the illness [8], and mortality ranges from less than 1–5.4%. While some drugs may prevent the progression to critical illness and mortality, their use should be timely [9, 10], so that the development of a prognostic tool with enhanced ease of use, speed and accuracy may be of paramount importance to prevent such outcomes.

In this scenario, a series of prognostic scales have been developed to predict either the potential for mortality or for aggravating disease, but they are not accurate [11, 12], are published in non-peer-reviewed
journals [13], are developed after small samples [14], are not COVID-19-specific [15] or only predict mortality [16]. We think that in order to enhance the capacity of healthcare workers to optimize the use of hospital resources, including regular and ICU beds, or the administration of life-saving drugs that are either expensive or scarce, three prognostic tools should be developed: one to predict the need for hospitalization, another to predict the need for intensive care (IC), and lastly one to predict the potential for mortality.

2. Materials And Methods

We gathered a total of 399 clinical files belonging to patients that were hospitalized at Sociedad Española de Beneficencia and Hospital Español, from March 12th 2020 to August 1st 2022 after COVID-19. The records were screened for the following inclusion criteria: (i) patients with confirmed SARS-CoV-2 infection (positive PCR, rapid antigen, IgM and/or CORADS 4), (ii) files that showed laboratory evaluations in the first 24 hours after hospital admission, (iii) patients with signed informed consent for the study. Then the records that complied with one or more of the following exclusion criteria were eliminated: (i) voluntarily-discharged patients, (ii) patients with clinical files lacking crucial information, (iii) post-COVID-19 care patients, and (iv) patients that were referred from other institutions and therefore had incomplete records.

Relevant data about markers that were previously associated with severe COVID-19 were collected on a Google Docs file, sorting the patients according to three different outcomes: mortality, intensive care requirement (ICR) and hospitalization requirement (HR). Mortality was defined as death occurring within hospitalization; ICR was defined as the use of the ICU staff and facilities for at least one day; and HR was defined as patients requiring a respiratory support superior to 5 L/min for at least one day (because this requirement is most likely unsustainable in an at home treatment setting).

The control patients were those that did not develop HR, ICR or did not died within the hospital, and are respective to each outcome measured. The percentage of lung infiltration was evaluated as described elsewhere [17–19] using the Chest CT Score. Briefly, chest computed tomography studies were evaluated by two independent researchers whom divided the lungs into five anatomical regions (one for each lobule), and assigned each one up to five points depending on the percentage of the parenchyma that was infiltrated, adding the points at the end.

The level of association of each marker with the three different outcomes was initially assessed by calculating the odds ratio (OR), considering as normal value ranges for each those published elsewhere [20]. Markers were considered to have a significant association with a particular outcome when $p \leq 0.05$. Then, the patients’ values were transformed in a binary manner, considering their value as “0” when they did not surpassed their reference values, and as “1” when they did. The binary data for significant associated markers was used to perform a Pearson’s correlation to estimate their weight, but only those that had a Pearson’s correlation index $\geq 0.20$ were integrated into the pertinent algorithm. These
consisted on the addition of the function of each marker (Pearson's index) when the patient exceeded the marker's reference values.

The individual patient's outcome predictor (OP) values were calculated and plotted into a Receiver Operating Characteristic (ROC) curve to estimate the sensitivity of each algorithm in the prediction of the aforementioned outcomes. Furthermore, the mean and standard deviation of the control group (negative for each outcome) were added, while the standard deviation was deducted from the mean of the outcome-positive group, and the middle point between each operation's results was found to calculate the cutoff value. Sensitivity (SE), specificity (SP), positive (PPV) and negative predictive (NPV) values, as well as the OR and Chi² values were then calculated to investigate each algorithm's characteristics.

All the statistic tests were performed and graphed using GraphPad Prism X9, and significant differences were considered when \( p \leq 0.05 \).

A protocol for this study was evaluated by the Institutional Committee of Research Ethics of the Sociedad Española de Beneficencia (Pachuca, Hidalgo) and the study was approved on February 24th of 2020. Our sponsor had no role in study design. All methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki, and written informed consent was obtained from all the patients studied.

3. Results

We assessed a total of 467 clinical files belonging to patients that were hospitalized at Sociedad Española de Beneficencia and Hospital Español, from March 12th 2020 to August 1st 2022. All files were analyzed, and upon assessment 422 were found to be suitable for analysis. 255 files were allocated to allow for algorithm design and 167 were used to validate the algorithms (Supp. Figure 1). The only criteria for such allocation was to use the files belonging to Hospital Español in the design of the algorithms, while the files from Sociedad Española de Beneficencia were used to test the scales with a different population. The patients whom contributed with the data for algorithm design were unvaccinated against SARS-CoV-2, while only 26% of the patients that provided data for the algorithms validation had already received such treatment.

Of the 255 clinical files that we used to calculate the algorithm 175 (74.5%) belonged to patients that were retrospectively found to have a justifiable hospitalization, while 59 (25.5%) did not develop characteristics that made hospitalization mandatory over their whole stay. Moreover, 125 (49.6%) patients required IC and 79 (31.1%) died at the hospital.

Given that severely affected chest tomography findings (% inf) [21], C-reactive protein (CRP), d-dimer, neutrophils, lymphocytes, lactate dehydrogenase (LDH) [22], procalcitonin, medium arterial pressure (MAP), creatinine, leukocytes, aspartate aminotransferase (AST) [23, 24], ferritin, oxygen saturation (sO₂) [25], advanced age and comorbidities [26] have been associated with COVID-19 progression, the exact values of these markers were extracted from the complete clinical files. Upon gathering the laboratory
data for the first 24 hrs of hospitalization, the OR for each of the markers was calculated in relation to HR (Supp. Table 1), ICR (Supp. Table 2) or mortality (Supp. Table 3). We found four significant associated markers (Kirby index, sO$_2$, CRP and LDH) with HR, 10 with ICR (d-dimer, neutrophils, % inf, age, Kirby index, sO$_2$, CRP, ferritin, LDH and AST) and 11 with mortality (creatinine, d-dimer, neutrophils, % inf, age, MAP, Kirby index, sO$_2$, CRP, ferritin, > 1 comorbidity and LDH).

The markers with significant associations were plotted into a heat map and their Pearson's correlation coefficient was calculated (Fig. 1a, c and e) and used to determine the relative weight, or mathematical function, of each variable into each of the three algorithms. Only four variables had a Pearson's correlation index $\geq 0.20$ in relation to each outcome, and thus were considered as important for the development of the algorithms, being Kirby$<200$, LDH$>211$, CRP$>120$ and sO$_2$$<80$ for the prognostic of hospitalization; Rx$>14$, Kirby$<200$, CRP$>120$, and LDH$>400$ for the prediction of ICR; and finally age$>60$, Kirby $<150$, CRP$>120$ and Rx$>15$ for mortality (Fig. 1b, d and f).

To calculate the OP for each patient, the Pearson's index of each variable (Fig. 1b, d and f) was added each time a particular patient presented an abnormal level of a particular marker, and then both control (outcome negative) and experimental (outcome positive) patients' values were used to calculate the area under the ROC curve (AUROC). The COVID-hospitalization outcome prognostic (COVID-HOP) scale had an AUROC of 91% (CI 0.8725 to 0.9482 at 95%, $p<0.0001$), and both the COVID-intensive care outcome prognostic (COVID-ICOP) and the COVID-mortality outcome prognostic (COVID-MOP) scales had an AUROC of 96% (CI 0.9448 to 0.9855 at 95%, $p<0.0001$ and CI 0.9464 to 0.9872 at 95%, $p<0.0001$, respectively) (Figure 2).

The cutoff value for the COVID-HOP scale was found to be 52.7, while the COVID ICOP was 113.1 and the COVID-MOP was 109 (Supp. Fig. 2). Thus, the complete algorithms with cutoff values were designed as detailed in Table 1, where the magnitude of function of each marker, given by the Pearson's correlation index, would add each time the patient presents pathological levels of it, and if the scale's cut-off value is exceeded the patient would be considered at risk of either dying, needing regular hospitalization or intensive care.

Table 1. Algorithms for COVID-HOP, COVID-ICOP and COVID-MOP calculations.
Furthermore, the SE, SP, PPV, NPV (Table 2) and OR (Supp. Fig. 3) for each OP scale with its respective cutoff value were calculated, finding that the COVID-HOP had a SE of 86%, SP of 74%, PPV of 90%, NPV of 94% and OR of 18.4 (CI at 95% 8.6 to 36, \( p \leq 0.0001 \)). On the other hand the COVID-ICOP had a SE of 87%, SP of 92%, PPV 92%, NPV of 88% and OR of 88.5 (CI at 95% 35-191, \( p \leq 0.0001 \)). Finally, the COVID-MOP has a SE of 92%, SP of 91%, PPV of 82%, NPV of 96% and OR of 131 (CI at 95% 47-341, \( p \leq 0.0001 \)).

<table>
<thead>
<tr>
<th>OP algorithms</th>
<th>COVID-HOP</th>
<th>COVID-ICOP</th>
<th>COVID-MOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirby index</td>
<td>&lt;200 = 67</td>
<td>&lt;200 = 66</td>
<td>&lt;150 = 67</td>
</tr>
<tr>
<td>Lactate dehydrogenase (LDH)</td>
<td>&gt;211 = 26</td>
<td>&gt;400 = 31</td>
<td>n.r.</td>
</tr>
<tr>
<td>Oxygen saturation (( sO_2 ))</td>
<td>&lt;80 = 26</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>&gt;120 = 31</td>
<td>&gt;120 = 36</td>
<td>&gt;120 = 30</td>
</tr>
<tr>
<td>Lung infiltration percentage (25 points scale on TAC)</td>
<td>n.r.</td>
<td>&gt;14 = 75</td>
<td>&gt;15 = 75</td>
</tr>
<tr>
<td>Age</td>
<td>n.r.</td>
<td>n.r.</td>
<td>&gt;60 = 22</td>
</tr>
<tr>
<td>If sum ( \geq 52.7 ), patient at risk</td>
<td>If sum ( \geq 113.1 ), patient at risk</td>
<td>If sum ( \geq 109 ), patient at risk</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: OP, outcome prognostic; HOP, hospitalization outcome prognostic; ICOP, intensive care outcome prognostic; MOP, mortality outcome prognostic; n.r., not-relevant.
Table 2
Sensitivity, specificity, positive and negative predictive values for the outcome prognostic scales.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect Size</th>
<th>CI at 95%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-HOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.8629</td>
<td>0.8040 to 0.9061</td>
<td>0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.7458</td>
<td>0.6220 to 0.8394</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.9096</td>
<td>0.8563 to 0.9445</td>
<td>0.0001</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.6471</td>
<td>0.5284 to 0.7500</td>
<td>0.0001</td>
</tr>
<tr>
<td>COVID-ICUOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.8710</td>
<td>0.8006 to 0.9190</td>
<td>0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.9291</td>
<td>0.8708 to 0.9623</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.9231</td>
<td>0.8603 to 0.9590</td>
<td>0.0001</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.8806</td>
<td>0.8148 to 0.9252</td>
<td>0.0001</td>
</tr>
<tr>
<td>COVID-MOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.9241</td>
<td>0.8440 to 0.9647</td>
<td>0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.9153</td>
<td>0.8649 to 0.9480</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.8295</td>
<td>0.7376 to 0.8939</td>
<td>0.0001</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.9643</td>
<td>0.9243 to 0.9835</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: HOP, hospitalization-outcome prognostic; ICOP, intensive care outcome-prognostic; MOP, mortality outcome-prognostic.

Furthermore, 167 patients’ records belonging to a different health center and that were not used to calculate the algorithms, were retrospectively studied to perform a validation of the SE, SP, PPV, NPV. Only 26% of these patients (32 individuals) were vaccinated against the coronavirus. The results for the MOP algorithm showed no variation in the second population tested, while the ICOP scale exhibited only minimal variation. In regards to the HOP algorithm, the specificity was considerably reduced (0.74 in the creation of the algorithm, 0.36 in the test of accuracy), but the other parameters remained without significant changes (Table 3).
## Table 3
Validation experiment for the HOP, ICOP and MOP algorithms.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect Size</th>
<th>CI at 95%</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-HOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.9398</td>
<td>0.8666 to 0.9740</td>
<td>0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.3684</td>
<td>0.2338 to 0.5272</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.7647</td>
<td>0.6737 to 0.8365</td>
<td>0.0001</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.7368</td>
<td>0.5121 to 0.8819</td>
<td>0.0001</td>
</tr>
<tr>
<td>COVID-ICOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.9365</td>
<td>0.8478 to 0.9750</td>
<td>0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.8596</td>
<td>0.7468 to 0.9271</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>0.8806</td>
<td>0.7817 to 0.9382</td>
<td>0.0001</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>0.9245</td>
<td>0.8214 to 0.9703</td>
<td>0.0001</td>
</tr>
<tr>
<td>COVID-MOP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.9241</td>
<td>0.8440 to 0.9647</td>
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<td>0.0001</td>
</tr>
</tbody>
</table>

### 4. Discussion

In the present research we assessed the degree of correlation of 16 biomarkers (three of them with 2 different reference limits) with three different outcomes (the future need for hospitalization and/or intensive care as well as the enhanced probability of mortality) by calculating the odds ratio, revealing six markers associated with the first outcome, 13 with the second, and 15 with the last. Nonetheless, when the data was binary transformed and analyzed by the means of a Pearson's correlation, only four markers were found to be associated with each marker: i) Kirby <200, LDH>211, sO2<80 and CRP>120 were highly associated with the requirement for hospitalization; Rx>14, Kirby<200, CRP>120, and LDH>400 were strongly related to the requirement for intensive care; and finally, age>60, CRP>120, Rx>15 and Kirby <150 correlated with a high mortality.

We then developed three different algorithms, all of them based on adding the Pearson's correlation index for the markers that were relevant to each outcome, every time a patient developed pathological levels of a particular molecule. Interestingly, when calculating the mathematical functions in biomedical sciences a common approach is to perform a nomogram [27], because of the underlying convenience of such
technique. Nonetheless, the precision of such a graphic tool is not remarkable. In these circumstances, the addition of the Pearson's coefficients may have helped to develop a series of tools with enhanced sensitivity, as the COVID-HOP, COVID-ICOP, and COVID-MOP algorithms showed a sensitivity over 90% in each case.

Currently, many meta-analysis [28-33] studying the risk factors and biomarkers for prediction of COVID-19 outcomes are available, but these are primarily based on cohort studies that are only representative of the Asian population, with minimal involvement of other genetic backgrounds. In this instance, the aforementioned studies’ results reflect an enhanced degree of similarity for all the clinical and laboratory findings. Nonetheless, when different populations are studied the level of association of some biomarkers with the disease outcomes varies [34, 35], in such a way that the evaluation of prognostic markers in different populations may be of paramount importance to enhance the sensitivity and specificity of a prognostic tool. In accordance to this line of thought, here we present results derived from the analysis of a Mexican population, that reflect key differences in the association of prognostic markers with outcomes of enhanced pathology, in which the absence of a positive correlation between comorbidities and the worsening of COVID-19 stands out.

However, in a validation experiment we observed that the degree of SE, SP, PPV, and NPV varied only in a slight manner, despite of using data belonging to patients of a different hospital, and with a quarter part of them having been vaccinated (a condition that was not present in the patients that provided the data for the elaboration of the algorithm). Further research is needed to confirm if such homogeneity is paralleled in an international cohort.

Overall, these results show the development of three tools that may aid in the administration of hospital resources, including regular hospital beds, intensive care unit beds, and drugs. Such technology may be of enhanced utility in the context of pandemic waves, which are expected to be a common occurrence in the coming years [36], especially since no vaccine formula has been proven to produce sterilizing immunoglobulin titers [37]. In fact, expert committees have agreed that healthcare digital innovations are both lacking [38] and necessary [39] to enhance hospital resiliency, thus making necessary the development of this kind of tools.

5. Abbreviations

ICU, intensive care unit; ICR, intensive care requirement; HR, hospitalization requirement; OP, outcome prognostic; ROC, receiver operator characteristics; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; IC, intensive care; %inf, extension of the inflammatory infiltrate of the lungs measured by tomography; CRP, C-reactive protein; LDH, lactate dehydrogenase; MAP, medium arterial pressure; AST, aspartate aminotransferase; sO2, oxygen saturation; AUROC, area under the ROC curve; HOP, hospitalization-outcome prognostic; ICOP, intensive care-outcome prognostic; MOP, mortality-outcome prognostic.
Declarations

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Conflicts of interest

None of the authors have any conflicts of interest to declare.

Contributions statement

ENO, AMA, LER, DAMF, AEES, ALA, ADM & ANP contributed to the design of the study, performed the statistical analysis and wrote the article; KGC, SHI, GRL, ARHR, DPO, SRS, DMO, JHM, SRP, MM, YLAC, NGC, ALGO, AMR, VGL, MCB, ADAA, ASG & EMF, acquired the data; BAVG & MJRM critically reviewed the manuscript.

Data availability statement

Data is available upon reasonable request to the corresponding author Alberto N. Peón at investigacion@benepachuca.com

References


**Figures**

![Figure 1](image)

**Figure 1**

Weights for the association between biomarkers and outcomes. The biomarkers with significant odds ratios were used to calculate the Pearson correlations with HR (a), ICR (c) and mortality (e). Pearson's indexes >0.20 were considered to be highly associated, and these indexes were taken as functions to calculate the enhanced probability of HR (b), ICR (d) and mortality (f).
Figure 2

Sensitivity of the COVID-19 outcome predictor scales. The area under the receiving operator characteristics curve was measured for the hospitalization (a), intensive care (b) and mortality outcome predictor algorithms (c). Abbreviations: ROC, receiving operator characteristics; AUROC, area under the ROC curve; HOP, hospitalization-outcome prognostic; ICOP, intensive care outcome-prognostic; MOP, mortality outcome-prognostic.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [COVIDOPSCIrepSupFig.docx](COVIDOPSCIrepSupFig.docx)