Simple Demographics and Laboratory Findings on Admission May Predict f In-hospital Mortality in Patients with SARS-CoV-2 Infection

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Abstract

Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection could result in different laboratory abnormalities. The prediction of the outcome based on simple demographics and laboratory parameters could be useful for clinical purposes. The objective of the study is to develop and validate a score (Covid19-score) based on demographics and laboratory findings, performed at hospital admission in patients with a SARS-CoV-2 infection confirmed on a reverse transcriptase-polymerase chain reaction of the nasopharyngeal swab, to predict in-hospital mortality.

Methods: Three cohorts of patients from three different hospitals were studied consecutively. The studied data came from patients' electronic records. On the basis of the retrospective analysis of the mortality in the developing cohort from the first hospital the cut-off points predicting in-hospital mortality for gender, age, hemoglobin, mean corpuscular volume, platelet count, leukocyte count, sodium, potassium, creatinine level, C-reactive protein level were found and Covid19-score as a sum of points was calculated for each patient. The area under the receiver operating characteristic curve (AUC) of the Covid19-score for predicting survival to hospital discharge was counted. The Covid19-score was validated using data of patients from a second hospital. The significance of Covid19-score was confirmed on the prospective cohort of patients collected from a third hospital,

Results: AUC of the Covid19-score for predicting survival to hospital discharge was 0.89 (0.84-0.95) $p<0.001$ in developing cohort, 0.850 (0.75-0.88) $p<0.001$ in validation cohort and 0.773 (0.731-0.816) $p<0.001$ in the prospective cohort.

Conclusion: The Covid19-score is useful in predicting the clinical outcome for hospitalized patients with SARS-CoV-2 infection

Background

Coronavirus Disease 2019 (COVID-19) is a current global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [1]. Its clinical spectrum ranges from asymptomatic infection to a severe or even fatal disease in some cases [2]. COVID-19 poses a challenge to healthcare systems. According to the WHO's data, COVID-19 has already spread worldwide, with over 74,879,038 confirmed cases, including 1,676,236 deaths as of December, 20, 2020 (https://www.who.int) [3]. The hospitalization rate is high and shortage of hospital Intensive Care Units (ICU) beds occurs in some countries [4]. The early stratification of mortality risk may help to make the decision to hospitalize a patient and to compare different treatment methods. Clinical evaluation of the patient on admission to hospital is one of the methods of risk stratification, often completed with demographics, laboratory and radiologic data [5–7]. Whereas, the evaluation of clinical data is susceptible to observer-dependent biases. Moreover, some data in real-life conditions may not be collected due to hospital personnel overwork [8]. Blood test are less prone to such biases. Laboratory tests provide results allowing for rapid decisions to be made about patient care; they also play an important role in the decision-making process in almost all diseases. Therefore, the scoring system to predict outcome in COVID-19 patients relying on simple demographics, hematological and biochemical parameters could be useful both for clinical practice and comparison of different treatment outcomes.

The aim of the study was to develop a simple scoring system (Covid19-score) based on demographics and basic laboratory parameters to predict outcome of hospitalized patients with COVID-19.

Methods

The study was approved by Bioethical Committee of the Wroclaw Medical University (number 275/2020). The collection of routine data to build an in-hospital mortality prediction model was retrospective and did not require the patient's written informed consent. The Bioethical Committee approved the publication of anonymized data.

Participants

The participants of the study came from 3 hospitals: County Hospital in Boleslawiec, Regional Specialist Hospital in Wroclaw and 4th Military Hospital in Wroclaw.

The developing cohort consisted of 129 patients of the County Hospital in Boleslawiec, Poland treated between March and July 2020. The validation cohort consisted of 239 patients of the Regional Specialist Hospital in Wroclaw, Poland treated between June and August 15, 2020. The prospective cohort consisted of 497 patients from the 4th Military Hospital in Wroclaw treated between October and December 2020. All the patients had SARS-CoV-2 infection confirmed by a positive result on a reverse transcriptase-polymerase chain reaction of the nasopharyngeal swab.

All studied patients were either discharged home, discharged to an isolation ward or to a nursing home, or died in hospital. In case of hospital transfers, lack of the studied laboratory parameters results or patients leaving the hospital against medical advice, the patient was not included in the study. The prospective cohort from the 4th Military hospital came from the hospital registry; all patients with a positive SARS-CoV-2 test from that registry were included in the study. In the course of the study, 628 patients were admitted and discharged from the hospital or died in the hospital. The patients without all studied laboratory parameters checked, patients who were transferred to another hospital, discharged against medical advice, or who left the hospital without being discharged, were excluded from the study. In the end, a total of 497 patients were included in the study and constituted the prospective cohort. The electronic medical records were searched to retrieve the following demographic data: age and gender, as well as the laboratory findings at hospital admission: hemoglobin level, mean corpuscular volume (MCV), platelet count, leukocyte count, creatinine level, C-reactive protein (CRP) level, potassium, and sodium level.

Risk assessment tool

Cut-off points for demographics and laboratory findings – set to distinguish between patients from the developing cohort who survived or died during hospitalization – were established using the Classifications and Regression Tree (CART) analyses. Global Cross Validation cost and its standard deviation were calculated. The individual Covid19-score was a sum of points obtained, where one point was assigned for each variable beyond one or more cut-off points. The area under the receiver operating characteristic curve (AUC) of the Covid19-score for predicting survival to hospital discharge was calculated in the developing, validation and prospective cohorts.

The cut-off points used in generating the scoring were calculated after obtaining the data from the developing cohort, before using them for analysis in the validation cohort. The cohort from the 4th Military Hospital was assessed as prospective cohort. This cohort consisted of the all consecutive COVID-19 patients eligible for the study and the scoring system was established before their admission to hospital.

Outcome

The outcome was survival to hospital discharge.

Statistical analysis

Continuous variables were presented as means and standard deviations or medians and interquartile ranges according to their distribution, and compared with Student's *t*-test or Mann Whitney U test. Discrete variables were presented as numbers and percentages and compared with chi-squared test. CART analysis was used to find cut-off points to differentiate survivors and non-survivors, and one point was given for each variable which is out of the range for survivors.

Scoring was based on the sum of the points obtained. Receiver operating characteristic (ROC) curve analysis was used for model validation.

P less than 0.05 was regarded as significant.

Results

The demographics and laboratory findings in the developing cohort, the validation cohort, and the prospective cohort were presented in Table 1.

Table 1
The demographics and laboratory findings.

Variable	Developing cohort N = 129	Validation cohort N = 239	Prospective cohort N = 497
Age (years)	71 (57–79)	67 (53–95)*	70 (56–81)#
Gender, male (%)	56 (43.0)	134 (56.1)	292 (58.8)*
Hemoglobin level, g/dL	12.9 (10.7–14.2)	13.6 (12.4–14.8)*	13.2 (11.8–14.5)*#
Mean corpuscular volume, fL	87.2 (83.6–91.1)	88.6 (86.2–91.5)*	90.2 (86.9–94.0)*#
Leukocyte count, 10^3/μL	6.8 (4.9–9.5)	6.2 (4.8–8.8)	8.1 (5.9–11.3)#
Platelet count, 10^3/μL	192 (151–258)	207 (168–259)	215 (167–287)
C-reactive protein, mg/dL	63.2 (18.5-132.7)	44.8 (10.0-102.1)	48.4 (10.2-123.5)
Creatinine, mg/dL	1.01 (0.76–1.54)	0.90 (0.75–1.12)	1.16 (0.93–1.53)
Sodium, mEq/L	135.7 (132.4-138.7)	140.9 (138.9-142.9)*	137 (134–140)*#
Potassium, mEq/L	4.1 (3.8–4.5)	4.2 (3.9–4.6)	4.0 (3.7–4.4)*#
*- p < 0.05 vs developing cohort			
#-p < 0.05 vs validated cohort			

The median age of studied cohorts was ranging between 67 and 71 years and the percentage of male participants was ranging between 43% and 58.8%.

The cut-off points for variables to predict in-hospital mortality in the developing cohort were presented in Table 2.

Table 2
The results of CART analysis for the cut-off points for variables to predict in-hospital mortality

Variable	A cut of point	Global Cross Validation cost;	SD of Cross Validation cost	Developing cohort	Validation cohort
				Beyond cut of point n (%)	Beyond cut of point n(%)
Age (years)	> 56	0.37	0.04	98 (76.0)	160 (66.9)
Gender, male	Male gender	0.43	0.05	56 (43.4)	134 (56.1)
Hemoglobin level, g/dL	< 10.55	0.61	0.04	30 (23.3)	28 (11.7)
Mean corpuscular volume, fL	> 92.9	0.41	0.04	20 (15.5)	46 (19.2)
Leukocyte count, 10^3/μL	> 9.635 or < 2.64	0.28	0.04	35 (27.1)	54 (22.6)
Platelet count, 10^3/μL	< 81.49 or > 315.5	0.44	0.04	30 (23.3)	46 (19.2)
C-reactive protein, mg/dL	> 51.14	0.32	0.04	72 (55.8)	111 (46.4)
Creatinine, mg/dL	> 1.115	0.31	0.04	49 (38.0)	50 (20.9)
Sodium, mEq/L	< 134.7 or > 145.4	0.51	0.04	57 (44.2)	28 (11.7)
Potassium, mEq/L	< 3.65 or > 6.255	0.45	0.05	20 (15.6)	27 (11.3)

The points for Covid19-score were: age above 56 years, male gender, hemoglobin below 10.55g/L, MCV > 92.9 fL, leucocyte count less than 2.64 or more than 9.635 10^3/μL, platelet count below 81.49 or above 315.5 10^3/μL, C-reactive protein above 51.14 mg/dL, plasma creatinine above 1.115 mg/dL, sodium below 134.7 or above 145.4 mEq/L, potassium level below 3.65 or above 6.255 mEq/L.

ROC curve of the Covid19-score in the developing cohort was presented in Fig. 2.

The AUC of the Covid19-score for predicting survival to hospital discharge was 0.89 (0.84–0.95) $P < 0.001$,

The AUC of the Covid19-score in the validation cohort was 0.850 (0.75–0.88) $P < 0.001$

(Fig. 3).

The ROC curve of the Covid19-score in the prospective cohort was presented in Fig. 4.

The Covid19-score and mortality rate in studied cohorts were presented in Table 3.

Table 3
Covid19-score and mortality in studied cohorts

Variable	Developing cohort N = 129	Validation cohort N = 239	Prospective cohort N = 497
Covid19-score median, IQR	3 (2–5)	3 (2–4)$	4 (3–5)&
Mortality rate n, (%)	45 (34.9)	45 (18.8)*	144 (29.0)#
* p < 0.001 vs developing cohort			
# p < 0.05 vs validation cohort			

The AUC of the Covid19-score in the prospective cohort was 0.773 (0.731–0.816) *P*< 0.001.

The Covid19-score was more sensitive than specific in the prediction of in-hospital mortality in hospitalized patients with SARS-CoV-2 infection (Table 4).

Table 4
The prospective cohort. Survivors and non-survivors in subgroups based on Covid19-score.

Covid19-score	Number of non-survivors	Number of survivors	True positive	False positives	False negatives	True negative	Sensitivity	Specificity
9	0	1	0	1	144	352	0.000	0.997
8	8	2	8	3	136	350	0.056	0.992
7	22	12	30	15	114	338	0.208	0.958
6	30	25	60	40	84	313	0.417	0.887
5	39	63	99	103	45	250	0.688	0.708
4	27	66	126	169	18	184	0.875	0.521
3	13	71	139	240	5	113	0.965	0.320
2	5	64	144	304	0	49	1.000	0.139
1	0	37	144	341	0	12	1.000	0.034
0	0	12	144	353	0	0	1.000	0.000

Based on the obtained results, a model was created to calculate the Covid19-score and the risk of death in patients with SARS-CoV-2 infection, as shown in Fig. 5 .

Discusion

The main finding of the study is that baseline demographic and laboratory findings can predict the outcome of treatment in hospitalized patients with SARS-CoV-2 infection. The created model of mortality risk assessment is

based on objective tests carried out on admission to the hospital. Early evaluation of in-hospital mortality is important, because if followed, it may improve health awareness of and facilitate the identification of high-risk individuals. Therefore, since it is related to the optimization of management strategies, learning the unfavorable factors is more important than simple forecasting.

In the COVID-19 era, many models for predicting in-hospital mortality have been built [9–22]. The data used to create them usually include age, gender, and selected elements of the treatments used, comorbidities, and results of radiological and laboratory tests. The collection of a detailed medical history sometimes is not easy to obtain, given that we focus on shortening patient contact time. The comorbidities are present in many mortality prediction models. Typically, the severity of a comorbidity is more significant than its presence itself. Therefore, we did not include comorbidities in the created model, as their impact is reflected in laboratory tests. We also did not include radiological screening, because, in clinical practice, a chest computed tomography is not a routine on-admission procedure used in patients with SARS-CoV-19 infection, especially given the circumstances of the pandemic. Oxygen saturation in room air is another important prognostic factor, but in real life, in patients undergoing oxygen therapy, it is difficult to obtain. The shortcoming of same prediction scores is inaccessibility of laboratory tests like ferritin or interleukine-6. Furthermore, risk scores developed in one population may not work in another, due to ethnicity variables, availability of treatment resources, and other, yet unidentified factors.

The presented risk score was developed as easy-to-implement and observe-independent, hence we decided to include only demographic data and basic laboratory tests.

As in other published reports, in this study, male gender is a factor that predisposes to the risk of death. Older age is also associated with a higher risk of death, as found by all authors of the COVID-19-related mortality study [10, 11, 13–16]. Age differences between cohorts in our study may be related to the different time of cohort formation. The tendency to admit patients to the hospital at the beginning of the epidemic was higher because the degree of risk related to COVID-19 infection was unknown [23].

The laboratory abnormalities in patients with COVID-19 disease are common. They could be related either to the disease itself, or to the comorbidities often leading to a severe course of COVID-19, such as: all types of malignancies, cardiovascular diseases, chronic kidney diseases, chronic obstructive pulmonary disease, obesity (BMI > 40), pregnancy, type 2 diabetes mellitus, sickle cell anemia and medications used.

Anemia, leukocytosis, increased CRP, creatinine, low or high sodium, potassium levels or platelet count is related to disturbed homeostasis and represents changes that could be related to SARS-CoV-2 infection or concomitant diseases and their treatments. The mortality in COVID-19 patients is higher when the comorbidities are present [5, 6, 15]. It should be stressed that the comorbidities often present as laboratory abnormalities even in patients without SARS-CoV-2 infection.

The significance of selected demographic and laboratory factors for the outcome is confirmed in many studies.

Anemia in patients with SARS-CoV-2 could be present before infection due to chronic illness, especially malignancies. Anemia could develop in the course of a SARS-CoV-2 infection by inflammation alone, including direct cytopathic injury of circulating erythrocytes or/and their bone marrow precursors due to infection, the damage due to hemolytic anemia, and/or thrombotic microangiopathy. The presence of anemia is related to increased mortality [24] which is concordant with the presented study.

In our study, surprisingly, higher MCV level is also related to the increased risk of mortality. The reason could be diseases which show increased MCV, such as hypothyroidism or vitamin B12 deficiency. However, further studies are required to assess whether elevated MCV level found during infection is the same as before the disease or not. The latter could indicate might result in MCV changes [25]. Inconsistently to our observation, the MCV in COVID-19 patients was lower than in healthy participants [26]. However, the MCV in non-survivors increased during hospitalization, resulting in mean MCV values similar to those presented in our study.

The leukocyte count is an important parameter used to predict the severity of COVID-19 disease [27]. Huang et al. found that ICU patients with COVID-19 disease had more leukocytes than non-ICU patients [28]. SARS-CoV-2 infection is primarily related to lymphopenia what may decrease leukocyte numbers, however, later on neutrophil count increases, leading to leukocytosis.

Increased CRP level and leukocytosis are signs of infection severity and according to the expectations are related to increased mortality [29, 30]. Increased CRP level is present in many risk scores predicting mortality in patients infected SARS-Cov2 but its cut-off point is different in various study populations [10, 13, 16–18, 21]. The CRP cut-off point established in this study was at 51.5 mg/dL.

The significance of platelet count for the outcome prediction was also studied in many groups of patients. In some other studies, platelets did not vary between survivors and non-survivors. However, the reason behind this could have been the presence of patients with both low and high platelets in the studied group; this, in turn, could lead to their normal average count [31]. Furthermore, Lippi et. al. found that thrombocytopenia is related to a higher risk of adverse events during hospitalization [32].

Hyponatremia is a common finding in pneumonia patients regardless of the etiology of the disease [33]. However, it is more prevalent in SARS-CoV-2 infected patients than in patients with pneumonia of other origins [34]. Our observation that hyponatremia is related to adverse outcomes in COVID-19 patients is concordant with other studies [35]. Hyponatremia is an outcome of various mechanisms, including an induction of the non-osmotic release of vasopressin by IL-6, which is increased in COVID-19 patients and inversely related to hyponatremia [36].

Hypernatremia, although rare, is also encountered in patients with SARS-CoV-2 infection and is related to higher mortality [37]. It may be the result of loss of free water due to perspiration. It may also be caused by abnormally increased renal sodium reabsorption due to increased angiotensin II activity, resulting from angiotensin-converting enzyme 2 receptors blockage by SARS-CoV-2 [38].

Hypokalemia is also commonly found in patients with COVID-19 pneumonia. Moreno-Perez reported that hypokalemia is a sensitive biomarker of adverse COVID-19 progression [39]. In the presented study, hypokalemia was a factor indicating poor outcome. Additionally, high potassium level was an unfavorable factor, which may be associated with renal failure and treatment with potassium-sparing drugs, which may be an indicator of comorbidities.

Creatinine level was the next predictor for adverse outcome. This is concordant with the findings of other authors [5, 10, 37]. Yang et al. reported that nearly 30% of COVID-19 patients with severe pneumonia showed increased creatinine [40]. High creatinine level in patients with COVID-19 may be a sign of their concomitant diseases, or may suggest that SARS-CoV-2 is able to induce kidney disease.

The validation cohort of the Covid19-score showed similar accuracy and prognostic results as the developing cohort. However, it could be noted that the two studied populations differed in terms of age and gender distribution. The difference may result from the hospitals' location: the developing cohort was hospitalized in a small town, while the validation cohort was hospitalized in a larger city, province capital. Furthermore, dialyzed patients with SARS-CoV-2 infection were admitted only to the hospital in Boleslawiec, where they were put on dialysis irrespectively of the presence of infection symptoms. Close accuracy of the Covid19-score in those two different populations indicates the significance of laboratory abnormalities.

The prediction of mortality of COVID-19 patients was assessed by other authors which used Chinese protocol severity classification, the pneumonia severity index (PSI), and Confusion-Urea-Respiratory Rate-Blood pressure-65 (CURB-65) in risk stratification and prognostic assessment. The AUC of the Chinese protocol severity classification, PSI, and CURB-65 was 0.735, 0.951, and 0.912. The AUC of the presented scores is similar to our study [23].

Studies based on results coming from a single laboratory facility had lower predictive accuracy. For example, lung ultrasound results did not predict mortality [12]. The degree of lung involvement may be considered important, but not critical to survival, which depends rather on body’s overall response to the infection.

In the presented study we do not exclude parameters that seem to be only borderline-related to mortality in the developing cohort. The significance of the assessed parameters may vary between different populations, therefore, the wider range of research makes it easier to predict the outcome. It is worth noting that the optimal cut-off slightly differs between the developing and validation cohorts. Furthermore, it is the same in developing and prospective cohorts. This finding may suggest that the importance of analyzed parameters differs in different populations – it needs further investigation.

The mortality in COVID-19 patients could be also related to the capabilities of the health care system, for instance early diagnosis, as the number of performed tests could play a significant role.

The clinical benefits of using the Covid19-score may be helpful in the pandemic period, when the number of patients requiring hospitalization is very high and it is necessary to list patients with a high risk of death upon admission. The particular value of the created scoring model is the fact that the model objective and based on simple diagnostic tools and methods widely available in all hospitals. The model might be especially useful in field and mobile hospital facilities. Such an initial assessment with the use of Covid19-score facilitates making decisions regarding the diagnostic and therapeutic management strategies in patients with SARS-CoV-2 infection. In addition, application of the Covid19-score could help compare the effectiveness of treatment using different methods.

Limitations

The main limitation of the study is the lack of clinical data related to comorbidities and treatment used. However, the aim of the study was to construct a simple threat-assessing score that could be used for individual patients even by professionals less familiar with clinical assessment of COVID-19 patients.

The other limitation is the lack of data regarding the time from the onset of the first symptoms to hospital admission. Laboratory findings could change in the course of the infection and the usage of the scores obtained

at the different points of the infection process may be not adequate.

The third problem was that the inclusion criterion for the study was a positive COVID-19 result during hospitalization. Some patients may be infected while hospitalized, and abnormal laboratory test results on admission may not necessarily point to a SARS-CoV-2 infection, but can be related to other diseases. SARS-CoV-2 infection can develop during hospitalization, also as asymptomatic. Additionally, some SARS-CoV-2 infections may not be revealed during the first smear test. Including only patients who had a positive test result on admission could omit such patients.

Conclusions

1. Basic demographic data and laboratory findings obtained upon admission from patients with SARS-CoV-2 infection may predict in-hospital mortality with good accuracy.

2. The optimal cut-off points for Covid19-score may be related to the differences in the studied populations.

3. Regardless of Covid19-score, the treatment at the tertiary Center was resulting in better outcomes, which requires further investigation.

Abbreviations

AUC: area under the receiver operating characteristic curve

COVID-19: Coronavirus Disease 2019

CURB-65: Confusion-Urea-Respiratory Rate-Blood pressure-65

CRP: C-reactive protein

ICU: Intensive Care Units

MCV: mean corpuscular volume

ROC: receiver operating curve

SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2

Declarations

Ethics approval and consent to participate.

The study was approved by Bioethical Committee of the Wroclaw Medical University - number 275/2020. The study was retrospective. Therefore, a consent to participate was waived by Bioethical Committee of the Wroclaw Medical University for this retrospective study.

All authors confirm that the study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials.

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request

Authors` contributions.

MO, DZ, KS conceived the idea of the study. MO, MPS, LB, DJ, KN, BJP, DZ, WB, KS contributed to research design. All authors were involved in data collection. MO, MPS, JW, DJ, KN, JM, JZJ, DZ analyzed the data. All authors edited and approved the final version of the manuscript

Competing on interests.

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Figures

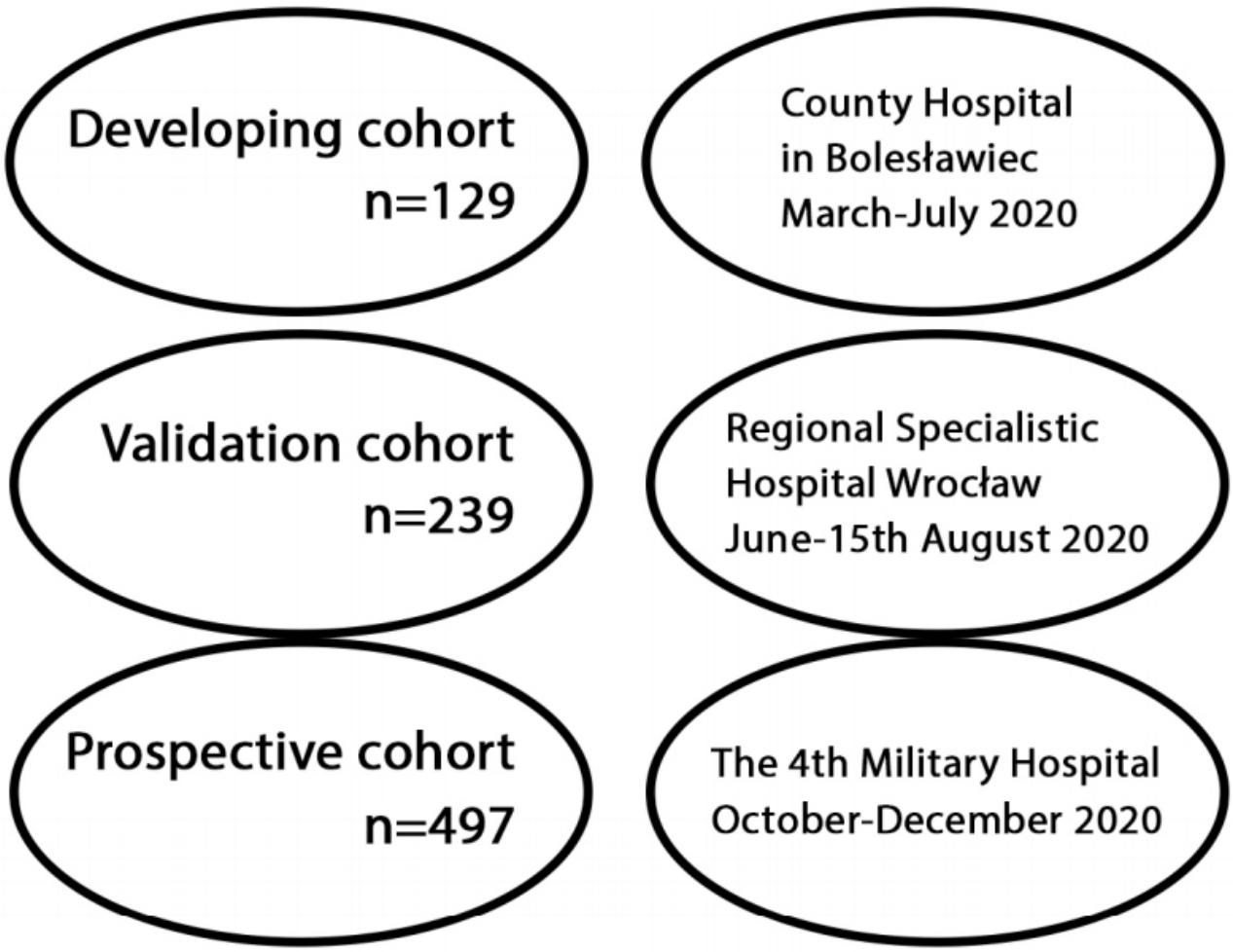

Figure 1

The design of the study

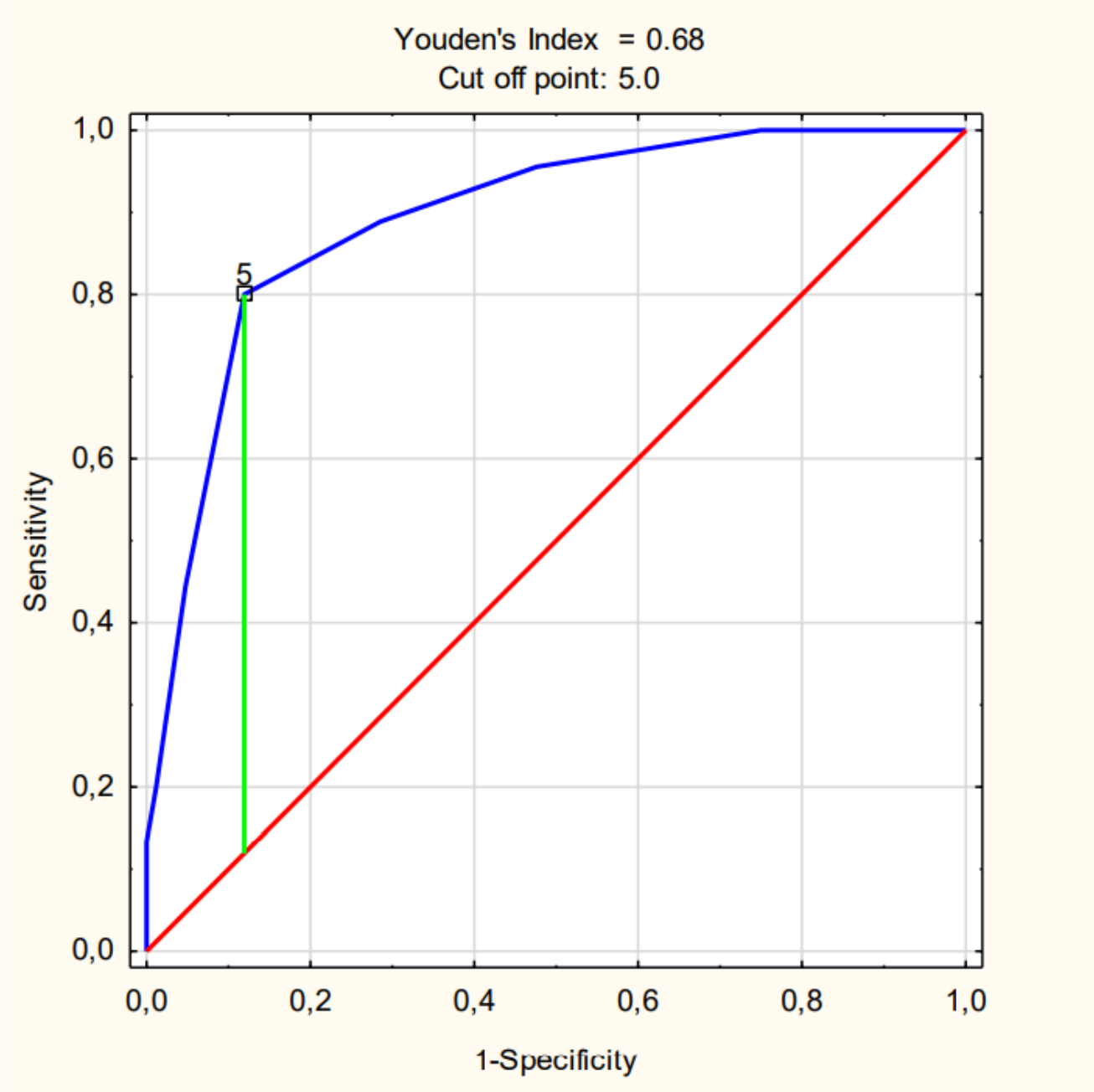

Figure 2

ROC curve for mortality prediction in developing cohort.

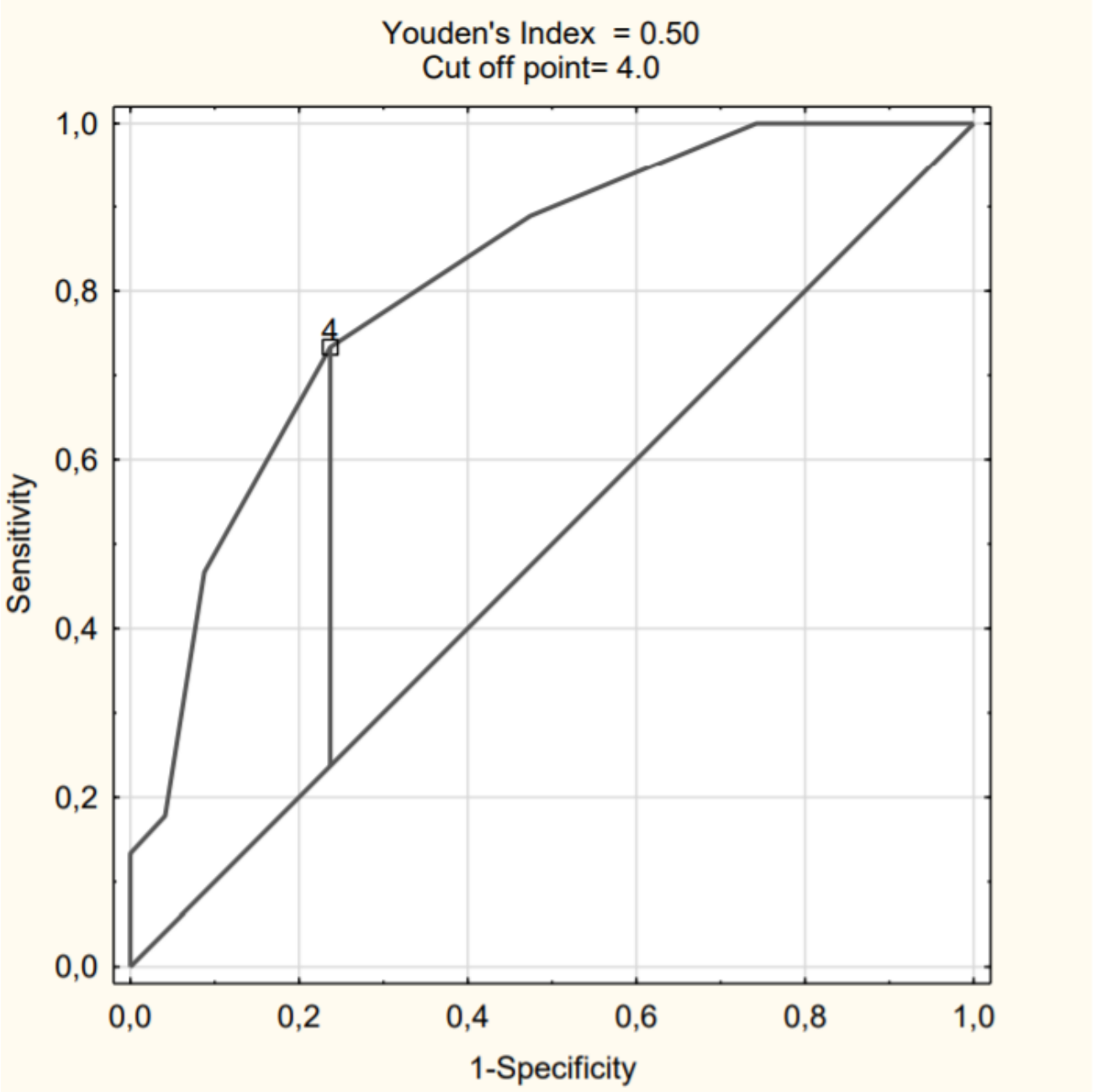

Figure 3

ROC curve for mortality prediction in validation cohort

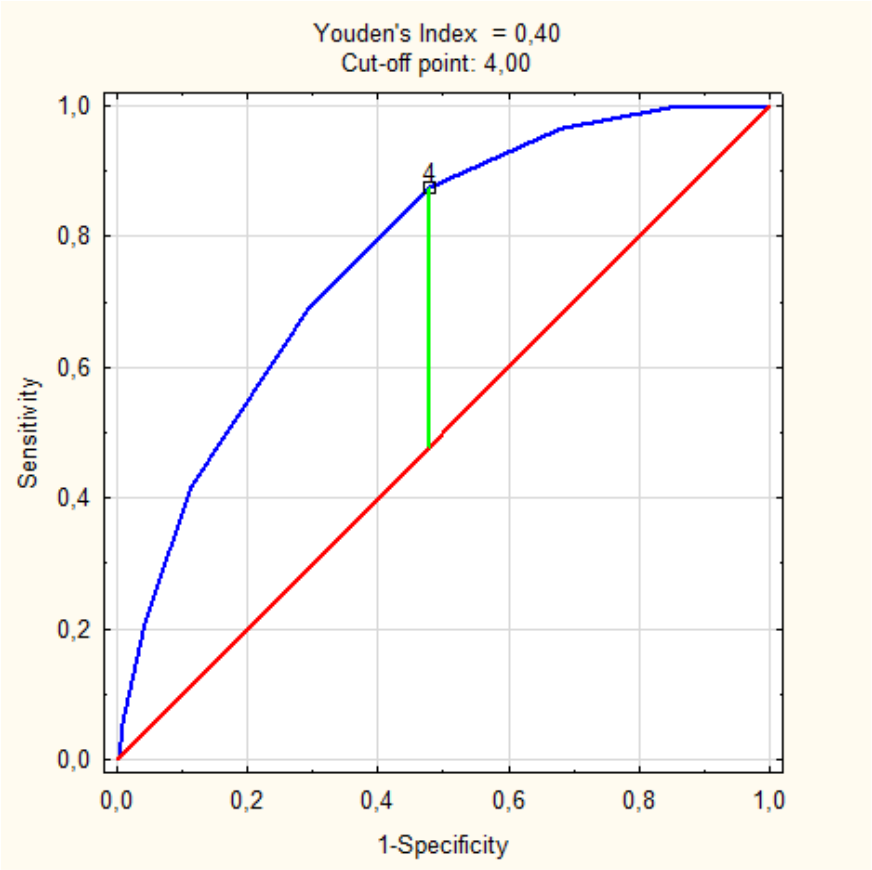

Figure 4

ROC curve for mortality prediction in prospective cohort

Predictor	Point
Age >56 years	1
Male gender	1
Hemoglobin level <10.55 g/dL	1
Mean corpuscular volume, >92.9 fL	1
Leukocyte count; >9.635 or <2.6410³/μL	1
Platelet count; <81.49 or >315.5 10³/μL	1
C-reactive protein; >51.14mg/dL	1
Creatinine, >1.115mg/dL	1
Sodium; <134.7 or >145.4 mEq/L	1
Potassium; <3.65 or >6.255 mEq/L	1

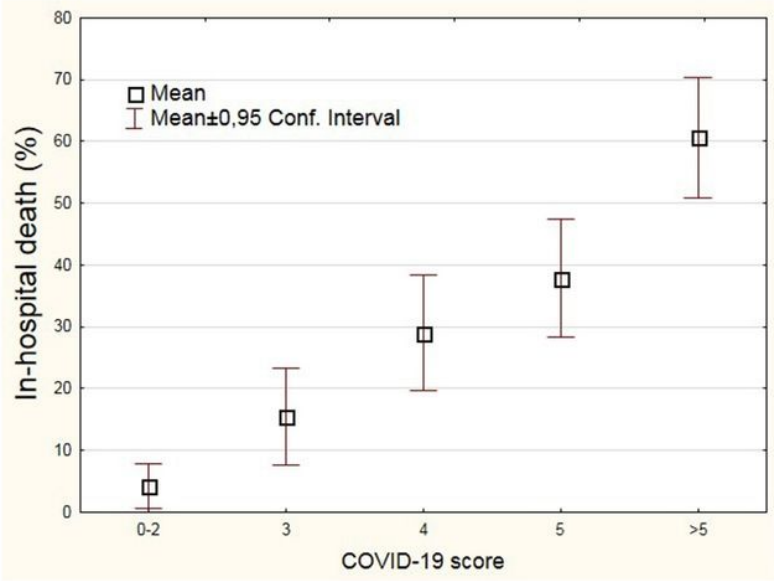

Figure 5

The method of calculating the Covid19-score and death risk based on the score. The Covid19-score is a total of points obtained for the presence of individual parameters.