The C2HEST score on admission to hospital may successfully predict the clinical outcomes of COVID-19 in all-comers population

Keywords
risk stratification, scale, SARS-CoV2, mortality

Abstract

Introduction
Since the beginning of SARS-CoV-2-pandemic, intensive efforts have been made to identify predictors of COVID-19 outcomes. Individual components of the C2HEST-scale, used to predict the risk of atrial fibrillation, reflect comorbidities presences. Therefore, we hypothesized that the score could predict unfavorable clinical COVID-19-outcomes.

Material and methods
2184-medical-records of subjects hospitalized at the medical-university-center due to COVID-19 from February 2020 to June 2021 were retrospectively analyzed . The subjects were categorized into low/medium/high-risk categories according to the C2HEST scale. Measured outcomes included: in-hospital-, 3-month- and 6-month-all-cause-mortality, the non-fatal hospitalization endpoints and other adverse in-hospital events.

Results
A total of 598 deaths (27.4%), including 326 in-hospital (15%) were reported. All three types of mortality were highest in the high-risk C2HEST-stratum (35.4%, 54.4, and 56.9%), ,and lowest in the low-risk-stratum: (8.4%, 15%, and 37.5%), respectively. The receiver-operating characteristics revealed that C2HEST allows one to predict 1-month mortality with AUC30=70.7 and maintained at a similar level after 3- and 6-month-observation(AUC90=72.0 and AUC180=67). The p-value for the Log-rank test comparing survival curves was <0.0001. An increase of one C2HEST-point raised the overall death rate 1.4-fold. A change from the low- to medium category increased the death rate 3.4 times, while between the low- and high-risk-stratum the hazard-ratio was 5.0. The C2HEST-score also revealed predictive value for pneumonia, sepsis, cardiogenic-shock, myocardi-injury, acute heart failure, kidney/liver-injury, stroke, gastrointestinal-bleedings.

Conclusions
The C2HEST-score is usefull in predicting adverse COVID-19-outcomes in hospitalized subjects. The simplicity of this scale, based on the presence of comorbidities, may address medical needs in risk stratification of COVID-19- patients.

The C2HEST score on admission to hospital may successfully predict clinical outcomes of COVID-19 in the all-comers population.

Abstract

Introduction: During the SARS-CoV-2 pandemic, intensive efforts have been made to identify COVID-19-outcome predictors. The C2HEST score, used to predict the atrial fibrillation risk, reflect comorbidities presences. This study aims to demonstrate the usefulness of this score in predicting COVID-19-outcomes in hospitalized individuals.

Material and Methods: 2184 medical records of subjects hospitalized due to COVID-19 from February 2020 to June 2021 were analyzed. Subjects were categorized into low/medium/high-risk categories according to the C2HEST score. Outcomes included: in-hospital-, 3- and 6-month-all-cause-mortality, non-fatal hospitalization endpoints, and other in-hospital events.

Results: 598 deaths (27.4%), including 326 in-hospital (15%), were reported. All types of mortality were highest in the high-risk stratum (35.4%, 54.4%, 56.9%), and lowest in the low-risk stratum (8.4%, 15%, 37.5%), respectively. The ROC revealed that C2HEST allows one to predict 1-month mortality (AUC30 70.7) and maintained at a similar level after 3- and 6-month observation (AUC90 72.0 and AUC180 67). The p-value for the Log-rank test comparing survival curves was <0.0001. An increase of one-C2HEST-point raised the overall death rate 1.4-fold. A change from the low- to medium-risk increased the death rate 3.4 times, while between the low- and high-risk-stratum the hazard-ratio was 5.0. The C2HEST score also revealed predictive value for pneumonia, sepsis, cardiogenic shock, myocardial injury, acute heart failure, kidney/liver injury, stroke, and gastrointestinal bleeding

Conclusions: The C2HEST score can predict COVID-19-outcomes in hospitalized subjects. This score simplicity, based on comorbidities, may address medical needs in the risk stratification of COVID-19-patients.

Keywords: SARS-CoV2; mortality; score; risk stratification

Introduction

Since the beginning of the SARS-CoV-2 pandemic, intensive efforts have been made to identify predictors of the COVID-19 clinical course predictors [1,2]. Numerous triage tools, including risk scores, could support decision-making by combining clinical assessment data to predict the risk of adverse outcomes. Early identification of COVID-19 patients at high risk of developing critical illness is of paramount importance, as it can inform appropriate management and optimize resource allocation. The initially published studies were designed to assist in making appropriate medical decisions, nevertheless, the first prognostic models were characterized by a relatively high risk of bias. Additionally, these models relied on an extensive set of clinical data, including laboratory parameters, physical examination findings, and imaging diagnostics. Consequently, their implementation in the dynamic settings of COVID-19(+) wards was rendered impractical due to their unwieldy complexity. As far as the literature is concerned, the risk factors for severe COVID-19 or mortality have been demonstrated to include age, smoking, presence of comorbidities, such as heart failure, right ventricular dysfunction, pulmonary hypertension, COPD (chronic obstructive pulmonary disease), or diabetes [3,4]. Despite the identification of numerous risk factors for disease progression, the clinical course of infection in individual patients remains uncertain. COVID-19 commonly manifests with inflammatory changes in the lungs, but a broad spectrum of organ complications, including cardiovascular events, appears to be caused by a "cytokine storm" [5,6]. Elevated rates of thromboembolic events, MI (myocardial injury) and ACS (acute coronary syndromes), acute HF (heart failure), AKI

(acute kidney injury), and ALD (acute liver dysfunction), and blood pressure fluctuations further complicate the in-hospital course of COVID-19 [7,8].

Several years ago, a simple clinical score, the C2HEST (C2: CAD (coronary artery disease) /COPD; H: Hypertension; E: Elderly [Age ≥75]; S: Systolic HF; T: Thyroid disease) was introduced to predict incident AF (atrial fibrillation) with reasonably good discrimination and internal calibration. The C2HEST score algorithm found an utility in cardiovascular medicine for risk stratification and, to some extent, outcome prediction. Associations between components of the C2HEST score and adverse outcomes have previously been established, particularly in subjects with HFpEF (heart failure with preserved ejection fraction) [9]. Nevertheless, the role of this score in predicting COVID-19 outcomes, encompassing both fatal and non-fatal events, has remained unexplored. Given that individual components of the C2HEST score reflect comorbidities, we assumed that C2HEST might hold promising predictive value for adverse clinical outcomes in COVID-19. Liang et al. were the first to demonstrate that the number of comorbidities predicted critical illness in hospitalized patients [10], which prompted us to investigate the predictive potential of the C2HEST score within the COVID-19 cohort.

Consequently, this study conducted a post-hoc analysis of the hospitalized COVID-19 patients as part of the COronavirus in LOwer Silesia (COLOS study) to assess the prognostic efficacy of the C2HEST score in predicting the outcomes, including mortality and non-fatal clinical events during hospitalization.

Material and Methods

Study design and participants

We analyzed the medical records of individuals admitted to a medical university center for COVID-19 between February 2020 and June 2021**.** The study protocol for the COLOS study received approval from the Institutional Review Board and Ethics Committee at Wroclaw Medical University, Wroclaw, Poland (No: KB-444/2021). As the data collection was retrospective, written informed consent was not required.

All patients were admitted with COVID-19 symptoms and a positive SARS-CoV-2 test result, following the testing protocol outlined by the WHO (World Health Organization). Nasopharyngeal swab specimens were obtained from all patients, and the presence of SARS-CoV-2 RNA was determined by strictly adhering to the manufacturer's instructions.

The analyzed data included demographic and clinical characteristics, respiratory support, smoking status, comorbidities, home medication, laboratory results, and the course of hospitalization. Adverse clinical events such as shock, PE (pulmonary embolism), DVT (deep vein thrombosis), MI, myocardial injury, acute HF, stroke/TIA, pneumonia, complete RF (respiratory failure), SIRS, sepsis, AKI, ALD, MODS, and bleeding were also recorded.

Follow-up and Outcomes

Commencing on the day of hospital admission and concluding on the day of discharge or demise, the follow-up period encompassed the entire duration of hospitalization. After the initial analysis, additional information regarding patient deaths was obtained on the 90^{th} and 180^{th} days following the day of admission. Patient characteristics were derived from individual clinical records.

The evaluated outcomes included: the in-hospital mortality, 3-month and 6-month all-cause mortality, and cessation of hospitalization not resulting from death (such as discharge to home, emergency transfer to another center due to deterioration, or transfer for rehabilitation). As secondary outcomes, the requirement for mechanical ventilation support, MI, shock, acute HF, PE, stroke, AKI, ALD, pneumonia, sepsis, SIRS, MODS, and incidences of bleeding were analyzed.

C2HEST score stratification

A cohort of 2184 subjects was included, and baseline patient characteristics has been extracted from the dataset to compute the C2HEST score, consisting of six individual components: CAD (1 point), COPD (1 point), hypertension (1 point), elderly status (age ⩾75 years, 2 points), systolic HF (2 points), and thyroid disease (1 point). It is essential to highlight that the criterion for CAD was satisfied by a positive history of MI or coronary revascularization (scored as 1 point). Furthermore, in subsequent sensitivity analyses, the term "thyroid disease" was more precisely defined as "hyperthyroidism" and "hypothyroidism." Subsequently, subjects were stratified into one of three primary risk categories: low risk (0-1 points), medium risk (2-3 points), and high risk (⩾4 points).

Statistical analysis

Descriptive data are presented as numbers with percentages for categorical variables, while numerical variables are expressed as means with standard deviation, range (minimum to maximum), and the count of non-missing values. An Omnibus test was employed for categorical variables with more than 5 expected cases in each group, and the Fisher exact test was utilized for cases with fewer cell counts. Welch's ANOVA was conducted for continuous variables due to unequal variances between

risk strata, with the sample size considered large enough for the appropriateness of asymptotic results. Post-hoc analysis for continuous variables utilized the Games-Howell test with Tukey correction, and for categorical variables, the post-hoc test mirrored the omnibus test, nevertheless was performed in subgroups including the Bonferroni correction.

In-hospital mortality and all-cause mortality were treated as right-censored data, leading to a time-dependent ROC analysis with IPCW (Inverse Probability of Censoring Weighting) estimation for these variables. The C2HEST score was evaluated through the time-dependent AUC (area under the curve), and survival curve differences between risk strata were confirmed using the log-rank test. The proportional hazard assumption was assessed with the Grambsch-Therneau test. A Cox proportional hazard model was employed to analyze the HR (hazard ratio) for the C2HEST score, its components, and risk strata.

For secondary outcomes, a logistic regression model was employed due to their dichotomic nature. Classical ROC analysis was performed, and the AUC measure was used to evaluate predictive capabilities. The OR (odds ratio) served as the effect size for the influence of the C2HEST score, its components, and risk strata.

All statistical analyses were executed using R version 4.0.4 with packages time-ROC, pROC [11], survival [12], coin [13], and odds ratio [14]. A significance level of 0.05 was chosen for all statistical analyses.

Results

Baseline characteristics of the studied population and comorbidities

Subjects within the low-risk C2HEST stratum exhibited the youngest age, the lowest prevalence of cigarette smoking, and a lower burden of comorbidities. Noteworthy, the prevalence of asthma did not exhibit significant differences between groups (Table 1 and Additional file 1).

Table 1. Baseline characteristics of the C2HEST risk-stratified study cohort

	Low risk [0-1]	**Medium risk [2-3]**	**High risk [>4]**	**Omni-bus p-*value***	**p-*value* (for post-hoc analysis)**
variables, units (N)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)		
Demographics					
age, years (2184)	51.1±15.9 17-74 (1418)	75.6±11.7 29-100 (492)	78.6±9.4 38-100 (274)	<0.0001	<0.0001[a, b] 0.0003[c]
≥ 65 years (2184)	376/1418 (26.5%)	419/492 (85.2%)	252/274 (92%)	<0.0001	<0.0001[a, b] 0.0259 [c]
male sex (2184)	735/1418 (51.8%)	208/492 (42.3%)	139/274 (50.7%)	0.0012	0.00095[a], 1.0[b], 0.088 [c]
BMI, kg/m2 (554)	28.3±5.1 15.4-49.4 (397)	29.3±5.6 18.6-47.8 (90)	27.8±5.8 16.4-48.2 (67)	0.210	N/A
BMI <18.5 kg/m2 (554)	3/397 (0.8%)	0/90 (0.0%)	2/67 (3.0%)	0.1882	N/A
BMI ≥30 kg/m2 (554)	132/397 (33.2%)	38/90 (42.2%)	21/67 (31.3%)	0.1882	N/A
smoking never/previous/current (2180)	(1338/1418 (94.4%) 46/1418 (3.2%) 34.1418 (2.4%)	431/489 (88.1%) 35/489 (7.2%) 23/489 (4.7%)	218/273 (79.9%) 36/273 (13.2%) 19/273 (7.0%)	<0.0001	<0.0001[a, b], 0.0216 [c]
Co-morbidities					
hypertension (2184)	416/1418 (29.3%)	357/492 (72.6%)	249/274 (90.9%)	<0.0001	<0.0001 [a, b, c]
DM (2182)	209/1418 (14.7%)	146/419 (29.7%)	118/273 (43.2%)	<0.0001	<0.0001 [a, b, c]
dyslipidemia (826)	289/418 (69.1%)	174/233 (74.7%)	148/175 (84.6%)	<0.0005	0.48[a], 0.0005[b], 0.064[c]
AFib/AFL (2184)	49/1418 (3.5%)	106/492 (21.5%)	135/274 (49.3%)	<0.0001	<0.0001[a, b, c]

past coronary revascularization (2184)	6/1418 (0.42%)	37/492 (7.5%)	111/274 (40.5%)	<0.0001	<0.0001[a, b, c]
past MI (2184)	11/1418 (0.8%)	63/492 (12.8%)	117/274 (42.7%)	<0.0001	<0.0001[a, b, c]
HF (2184)	0/1418 (0%)	53/492 (10.8%)	202/274 (73.7%)	<0.0001	<0.0001[a, b, c]
moderate or severe VHD/valve surgery (2184)	13/1418 (0.9%)	32/492 (6.5%)	51/274 (18.6%)	<0.0001	<0.0001[a, b, c]
PAD (2184)	26/1418 (1.8%)	31/492 (6.3%)	43/274 (15.7%)	<0.0001	<0.0001[a, b, c]
past stroke /TIA (2184)	47/1418 (3.3%)	59/492 (12.0%)	58/274 (21.2%)	<0.0001	<0.0001[a, b], 0.00312[c]
CKD (2184)	70 /1418 (4.9%)	70/492 (14.2%)	91/274 (33.2%)	<0.0001	<0.0001[a, b, c]
hemodialysis (2184)	19/1418 (1.3%)	20/492 (4.1%)	19/274 (7.0%)	<0.0001	<0.0001[a, b], 0.356 [c]
asthma (2184)	54/1418 (3.8%)	20/492 (4.1%)	11/274 (4.0%)	0.962	N/A
COPD (2184)	6/1418 (0.4%)	25/492 (5.1%)	44/274 (16.1%)	<0.0001	<0.0001[a, b, c]
hypothyroidism (2184)	76/1418 (5.4%)	68/492 (13.8%)	64/274 (23.4%)	<0.0001	<0.0001[a, b], 0.0035[c]
Hyperthyroidism (2184)	4/1418 (0.3%)	10/492 (2.0%)	7/274 (2.6%)	<0.0001	0.0013[a], 0.0015[b], <0.0001[c]

Continuous variables are presented as mean ± SD, range (minimum-maximum), and number of non-missing values. Categorized variables are presented as a percentage. Information about the numbers with valid values can be found in the left column. Abbreviations: N–valid measurements, n–number of patients, SD–standard deviation, BMI–body mass index, DM–diabetes mellitus, AF/AFL–atrial fibrillation/flutter, MI–myocardial infarction, HF–heart failure, PAD–peripheral artery disease, TIA–transient ischemic attack, CKD–chronic kidney disease, COPD–chronic obstructive pulmonary disease, VHD–valvular heart disease, N/A–not-applicable, a–*low*- vs. *medium*-risk, b–*low*- vs. *high*-risk, c–*medium*- vs. *high*-risk

Upon admission, individuals in the low-risk stratum presented higher prevalence of cough and smell dysfunction. In contrast, those in the high-risk C2HEST stratum reported more frequent dyspnea. Furthermore, the high-risk stratum was further characterized by the highest pulse pressure and the lowest SpO2 (blood oxygen saturation) on room air without respiratory support. Physical examination findings in the high-risk group included more frequent pulmonary obturation as well as congestion and higher VES-13 score values (Additional file 2).

Characteristics of In-hospital Laboratory Tests and Treatment Applied:

Laboratory Assays:

Consistently, the high-risk C2HEST group exhibited the lowest hemoglobin and platelet counts throughout the whole observation period. Upon discharge, individuals in the high-risk stratum more commonly revealed lymphopenia and elevated neutrophil and leucocyte counts. Noteworthy, in the low-risk C2HEST stratum, the CRP level decreased, whereas it increased in the high-risk group. Interestingly, no significant differences between the groups in IL-6 and ESR levels, both at baseline and discharge, were noted. Individuals in the higher-risk strata had higher d-dimer concentrations, lower prothrombin rate, and higher INR both on admission and discharge. Furthermore, baseline ferritin levels were lowest in the high-risk group on admission but increased at discharge, showing a rising trend unique to this stratum. Parameters of kidney function, including urea, creatinine, and eGFR, remained significantly worse in the high-risk C2HEST stratum throughout the hospitalization period, and total protein and albumin levels remained the lowest in this group. Troponin T and NT-proBNP levels were higher in the high-risk stratum throughout the observation period, and acute

myocardial injury was more common in this group. On admission, the high-risk group exhibited the lowest vitamin D levels, as well as the highest TSH and lowest fT3 concentrations (Additional file 3).

Specific treatment applied during the hospitalization period

No significant differences were observed in the use of systemic corticosteroids, remdesivir, tocilizumab, or convalescent plasma between the different C2HEST risk strata. The notable distinction lay in the higher frequency of specific antimicrobial treatments administered to subjects in the high-risk C2HEST stratum (Additional file 4).

Supportive treatment applied during hospitalization

The need for oxygen supplementation, including high-flow nasal cannula and invasive ventilation, increased with the C2HEST score. Conversely, oxygenation parameters during the qualification for advanced respiratory support decreased. Moreover, the requirement for urgent coronary angiography and revascularization increased with the C2HEST score. The utilization of catecholamines was notably more common in the high-risk group. Interestingly, no significant differences were noted regarding the need for *de novo* hemodialysis (Additional file 5).

Outcomes

C2HEST score results and mortality

Out of the studied cohort of 2184 subjects, a total of 598 deaths (27.4%), including 326 in-hospital deaths (15%), were reported during the entire observation period. In-hospital mortality at the 3rd and

6th month following hospital admission was highest in the high-risk stratum and lowest in the low-risk stratum (Table 2).

Table 2. Total and in-hospital all-cause mortality in the C2HEST risk strata.

	Low risk [0-1]	**Medium risk [2-3]**	**High risk [>4]**		
Variables, units (N)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)	Omnibus *p-value*	*p-value* (for post-hoc analysis)
All-cause mortality rate					
In-hospital (2184)	119/1418 (8.4%)	110/492 (22.4%)	97/274 (35.4%)	<0.0001	<0.0001[a, b], 0.0004 [c]
3-month (2088)	201/1343 (15%)	198/475 (41.7%)	147/270 (53.6%)	<0.0001	<0.0001[a, b], 0.0031 [c]
6-month (1117)	214/571 (37.5%)	208/331 (62.8%)	156/215 (56.9%)	<0.0001	<0.0001[a, b], 0.0713 [c]

Categorized variables are presented as a percentage. Abbreviations: N–valid measurements, n–number of patients, SD–standard deviation, ANOVA–analysis of variance, N/A–non-applicable, a–*low*- vs. *medium*-risk, b–*low*- vs. *high*-risk, c–*medium*- vs. *high*-risk

Discriminatory performance of the C2HEST score on total and in-hospital all-cause mortality

Time-dependent receiver operating characteristic (time-ROC) analysis demonstrated that the C2HEST score enabled the prediction of 1-month mortality with an AUC_{30} value of 70.7, maintaining a similar level for 3- and 6-month observations (AUC_{90}=72.0 and AUC_{180}=67, respectively) (Figure 1A). The time-dependent AUC for predicting in-hospital deaths remained consistently above 60 throughout the whole hospitalization period, albeit relatively lower than those calculated for total mortality (Figure 1B). All the data was calculated for all-cause death without competing risk.

[insert fig.1]

Figure 1. Time-dependent receiver operating characteristic (time-ROC) curves for the C2HEST score in predicting total (A) and in-hospital mortality.

Similarly, the time-ROC analysis was performed to assess the predictive value of the C2HEST score for in-hospital (Figure 2A) and all-cause (Figure 2B) mortality at a particular time from admission to the hospital.

[insert fig.2]

Figure 2. Time-dependent ROC analysis for the C2HEST predictive abilities of all-cause death (A) and death during hospitalization (B) (AUC with CI).

Survival probability for hospitalized COVID-19+ subjects

Kaplan-Meier survival curves, based on the original stratification (low/medium/high for 0-1/2-3/⩾ 4 points, respectively), revealed a significant difference (p-*value* <0.0001) in survival probability among risk strata (Figure 3A). The estimated six-month survival probability for high-risk subjects was 0.4, while for low-risk subjects it remained above 0.8 throughout the entire observation period. Noteworthy, a similar analysis for in-hospital survival yielded comparable results (Figure 3B).

[insert fig.3]

Figure 3. Analysis of the survival curves (A) and in-hospital survival (B) for the low, medium, and high C2HEST risk strata (Kaplan-Meier curve, log-rank p-*value* <0.0001)

Risk-strata matching analysis

To ascertain the optimal risk stratification for differences in Kaplan-Meier survival curves, a comprehensive analysis of all possible C2HEST intervals was performed. The log-rank test statistics

revealed that the highest value was achieved for the primary risk categories: 0-1 (low), 2-3 (medium), and ≥4 (high) points. This analysis was reiterated for in-hospital mortality, yielding consistent results (Additional files 6 and 7).

Effect of C2HEST risk stratification on COVID-19 survival

Two Cox models have been analyzed to evaluate the effect of C2HEST score stratification on COVID-19 mortality. The overall model, considering the uncategorized C2HEST score, demonstrated that an increase of one point in the C2HEST score raised the total death intensity by approximately 40% (HR 1.399, 95% CI 1346-1453, p<0.0001). Transitioning from the *low* to the *medium* category increased death intensity 3.4-fold, and from *low*- to *high*-risk group, the hazard ratio was 5.1. A similar analysis for in-hospital deaths showed an increase in one point in the C2HEST score raising the in-hospital death intensity by 1.27-fold. Transitioning from *low* to *medium* category increased in-hospital death intensity by 2.3-fold, and from *low*- to *high*-risk group resulted in a HR of 2.96 (Table 3). Associations of individual C2HEST score components with mortality are detailed in Additional file 8. The Cox proportional hazard model for all-cause death and logistic regression models for other outcomes revealed that CAD and age exhibited the highest prognostic value for in-hospital mortality (Additional file 9).

Table 3. The total all-cause and in-hospital death for C2HEST risk stratification.

	Total deaths			**In-hospital deaths**		
Overall	HR	95%CI	*p-value*	HR	95%CI	*p-value*
	1.40	1.346-1.453	<0.0001	1.272	1.205-1.343	<0.0001
Risk strata						
Medium- vs. *low*-risk	3.43	2.808-4.091	<0.0001	2.315	-	-
High- vs. *low*-risk	5.10	4.086-6.136	<0.0001	2.960	-	-

Abbreviations: HR–hazard ratio

Associations of C2HEST score with other non-fatal outcomes

Detailed results of the associations of the C2HEST score with other non-fatal outcomes are presented in Additional file 4, 5, 10, and 11. The *high*-risk-C2HEST-stratum was associated with a higher prevalence of shock (an increase in one point raised the risk by 14% ($OR_{low\ vs\ high}$=1.64, 95%CI 1.07-2.46, p=0.0182). The strongest association was also observed for the cardiogenic shock ($OR_{overall}$= 1.63, 95%CI 1.38-1.92, p<0.000 and $OR_{low\ vs\ high}$= 10.85, 95%CI 4.47-28.88, p<0.001). Myocardial injury, acute HF, the need for coronagraphy and revascularization increased with the C2HEST score (for MI: the $OR_{overall}$=1.41, CI 1.17-1.70, p=0.0002 while $OR_{low\ vs\ high}$ =5.301, CI 1.93-14.52, p=0.0009). An increase in one point in the C2HEST score raised the risk for myocardial injury by 36.7% ($OR_{low\ vs\ high}$=4.18, 95%CI 2.95-5.94, p<0.0001), and for the onset of acute HF 2.03-fold (the $OR_{low\ vs\ high}$=35.56, 95%CI 15.50-82.27, p<0.0001). A similar tendency was observed for the occurrence of in-hospital stroke/TIA ($OR_{overall}$=1.24, 95%CI 1.07-1.44, p<0.001 and $OR_{low\ vs\ high}$=2.04, 95%CI=0.78-4.73, p<0.0001). The *high*-risk subjects had a 2-fold greater risk of development of complete RI when compared to the *low*-risk ones (the $OR_{overall}$=1.19, 95%CI 1.05-1.36, p=0.0083). Pneumonia was also more frequent in the *high*-risk stratum and an increase in one point in the C2HEST score resulted in a higher risk for pneumonia ($OR_{overall}$=1.28, 95%CI 1.21-1.36, p<0.001 and $OR_{low\ vs\ high}$=2.28, 95%CI=1.74-3.01, p<0.0001). An increase in one point in the C2HEST increased the risk for sepsis by 36% (the $OR_{low\ vs\ high}$= 3.37, 95%CI 1.31-10.23, p=0.01). The development of AKI and ALD was more common in higher C2HEST risk strata (for AKI: the $OR_{overall}$=1.31,

95%CI 1.23-1.41, p<0.0001, the $OR_{low\ vs\ high}$=1.86, 95%CI 2.74-4.56, p<0.0001; for ALD: the $OR_{overall}$=1.26, 95%CI 1.11-1.42, p=0.0003, the $OR_{low\ vs\ high}$=2.40, 95%CI 1.21-4.50, p=0.0084). Also, a higher C2HEST score was associated with a more common incidence of total and gastrointestinal bleeding and a longer duration of hospitalization. The increase in one point in C2HEST score raised the risk of upper gastrointestinal bleeding by 31% (the $OR_{low\ vs\ high}$=3.80, 95%CI 1.62-8.58, p=0.0015) (Additional file 11). The summarized discriminatory performance of the C2HEST score on the clinical events is presented in Additional file 12.

Sensitivity analysis

Results of the sensitivity analysis are summarized in Additional files 13 and 14. Modification of the C2HEST score definition, such as replacing "thyroid disease" with "lack of hypothyroidism" and adjusting the age cutoff to ">65 years" led to a significant increase in predictive value for various endpoints, including all-cause mortality ($HR_{overall}$=1.44, 95%CI 1.38-1.49, p<0.0001 and $HR_{low\ vs\ high}$= 6.65, 95% CI 5.16-8.58, p<0.0001). A one-point increase in the modified C2HEST score raised the risk for in-hospital death by 1.54-fold, whereas subjects from the modified *high*-risk stratum are at an 8.1-higher risk of in-hospital death. The modified C2HEST score demonstrated improved prognostic value for acute HF ($OR_{overall}$=1.99, 95%CI 1.75-2.28, p<0.0001 and $OR_{low\ vs\ high}$=36.73, 95% CI 11.3-224.52, p<0.0001), MI ($OR_{overall}$=1.49, 95%CI 1.23-1.82, p<0.0001 and $OR_{low\ vs\ high}$=10.83, 95% CI 3.223-65.45, p<0.0001), pneumonia ($OR_{overall}$=1.29, 95%CI 1.23-1.36, p<0.0001 and $OR_{low\ vs\ high}$=3.04, 95% CI 2.48-3.74, p<0.0001), AKI ($OR_{overall}$=1.35, 95%CI 1.26-1.45, p<0.0001 and $OR_{low\ vs\ high}$=4.51, 95% CI 3.11-6.68, p<0.0001). The ROC curves for the modified C2HEST score

(C2HEST-COLOS) are presented in Additional file 15. The area under the receiver operating curves determined for individual predictors amounted to 0.622 - 0.865 (for pneumonia and acute heart failure, respectively).

Discussion

This is the first study to demonstrate the usefulness and performance of the C2HEST score in predicting adverse COVID-19 outcomes in hospitalized all-comers population, including death, cardiovascular complications, pneumonia, the need for mechanical ventilation, acute liver and kidney injury, or gastrointestinal bleedings. Our results show that the C2HEST score, when analyzed both categorically and continuously, has a potent predictive ability for adverse outcomes. The C2HEST score is well-recognized among clinical practitioners in cardiovascular and internal medicine. Its simplicity and ease of obtaining the variables constituting its components indicate a potentially wide range of practical applications. Appropriately triaging individuals who are initially at higher risk for complications, particularly cardiovascular ones, and/or poor outcomes is crucial in decision-making processes, especially in situations with limited resources.

Notably, the C2HEST score did not correlate with the prediction of SIRS, MODS, and deep vein thrombosis. Despite this fact, it maintained a high level of discrimination in predicting all-cause in-hospital mortality, post-hospital total mortality, as well as numerous adverse clinical events.

Despite the growing body of literature on COVID-19 outcomes, predicting mortality remains a difficult challenge. The initial management of individuals hospitalized with COVID-19 involves assessing the risk of adverse outcomes and the need for life-saving intervention. This assessment helps

make the informed decisions regarding hospital admission and inpatient referrals. Therefore, the use of an appropriate clinical score upon hospital admission to predict which COVID-19 patients will develop critical illness is crucial and may significantly impact future outcomes. So far, several score systems have been introduced to predict adverse COVID-19 outcomes, including the PRIEST score [15], Brescia COVID Severity Scale (BRCSS) [16], COVID-Gram Risk Score [10], and VACO index [17]. Nevertheless, most of them derive from extensive clinical data, including laboratory parameters, physical examination findings, or imaging diagnostics data, which makes them extremely complex and less practical for everyday clinical use. Hence, the simple, validated risk-scoring systems with at least moderate predictive value are still lacking. The age of patients has consistently emerged as a strong predictor of COVID-19 mortality [18, 19, 20], and it is among the most robust indicators of poor outcomes. Previous studies have also examined individual comorbid conditions such as CAD, COPD, diabetes, and hypertension [21, 22, 23] as potential risk factors for a severe course of COVID-19. Liang et al. were the first to demonstrate that considering the count of multimorbidity may provide better predictive value than analyzing a single disease one by one [10]. This rationale led to the implementation of the C2HEST score for predicting the severity of COVID-19 in individuals. In our study, the analysis of the univariate Cox proportional hazard model for all-cause mortality and the competing risk regression model for non-fatal clinical events confirmed the strongest predictive value for age and CAD when analyzed as individual components of the C2HEST score. The modification of the C2HEST score in the COLOS study, which included the substitution of "thyroid disease" with "lack of hypothyroidism" and a more liberal cutoff point for age (>65 instead

of the initial >75 years), increased its predictive value for in-hospital mortality and most adverse clinical events. We suggest that such a straightforward modification of the score, as presented in this study, should be considered in the risk stratification of hospitalized COVID-19 patients.

Interestingly, both the C2HEST and C2HEST-COLOS scores demonstrated relatively higher prognostic values for adverse non-fatal cardiovascular events, including MI/myocardial injury and HF, as well as stroke when compared to SIRS, sepsis, or septic shock. Since the components of this score primarily consist of cardiovascular risk factors and cardiovascular disorders, its prognostic value for events attributed to inflammation or coagulopathies may be underestimated. This highlights potential limitations of the C2HEST score, necessitating additional clinical risk assessments, including laboratory parameters for inflammation and coagulation. It is worth noting that statistically significant differences in specific comparisons between the moderate and severe risk strata were less frequent. Therefore, the utility of the C2HEST score in predicting the risk of clinical events such as MI, stroke, sepsis, and ALD during COVID-19 is primarily attributable to differences between the low-risk vs. other risk groups. Furthermore, statistical analysis revealed relatively high 3- and 6-month mortality rates in the low-risk group. Noteworthy, these rates remain significantly lower in the low-risk group compared to the moderate and high-risk groups, which is the basis for the usefulness of the C2HEST score This observation may be explained by the initial selection of patients upon hospital admission, where individuals with mild illness were treated on an outpatient basis, leading to a relatively high

overall mortality rate among hospitalized COVID-19 patients. Nonetheless, the simplicity and prognostic value of the C2HEST score for predicting all-cause mortality and various adverse events may justify its validity for risk assessment.

According to the results of our study, using the C2HEST score to triage patients upon hospital admission based on multimorbidity enables the prediction of both mortality and clinically significant non-fatal adverse events. Given the unpredictable nature of the disease progression and the sudden onset of complications, clinicians may find surprising the need for urgent admission to the intensive care unit or the development of acute organ dysfunction. Our study illustrates that the C2HEST score could serve as a straightforward and valuable tool for clinicians to predict the outcomes of hospitalized COVID-19 patients, facilitating diagnostic and therapeutic decision-making. Individuals categorized into the high-risk C2HEST stratum could benefit from more intensive monitoring. The score could facilitate decisions regarding early transfers to specialized ICU units and the implementation of preventive strategies, potentially averting advanced organ damage.

Additionally, in the CAD cohort, the C2HEST score had predictive value for acute heart failure and hypovolemic shock. However, in the non-CAD cohort, it enabled the prediction of cardiovascular disorders (such as cardiogenic shock, myocardial injury, MI, acute HF episodes, stroke, or TIA), all types of bleeding, acute AKI, and ALD, along with infection complications like pneumonia and sepsis [24]. Noteworthy, the C2HEST score's predictive ability in the HF cohort failed to demonstrate discriminatory performance for mortality and other clinical adverse outcomes during hospitalization. This could be attributed to the fact that HF itself is a strong risk factor for poor COVID-19 outcomes

when hospitalization is required. Conversely, in the non-HF cohort, the C2HEST score exhibited significantly better performance in predicting in-hospital and 6-month mortality, as well as other non-fatal clinical outcomes, including cardiovascular events (myocardial injury, acute HF, MI, cardiogenic shock), pneumonia, sepsis, and AKI [25].

Diabetes mellitus, in addition to HF and CAD, is an independent risk factor for worsening the course and mortality of COVID-19, as demonstrated in multiple studies [26, 27, 28]. In the diabetic cohort, a 1.82-fold higher mortality rate was observed when compared to patients with normal glycemia levels. Interestingly, the mortality risk significantly increased across higher C2HEST strata, irrespective of the presence of glucose metabolism abnormalities. [29]. Information on risk factors such as diabetes or smoking, which are not included in the C2HEST score, could also be easily obtained from patients upon admission. We believe that incorporating these factors into the assessment of disease risk could be highly significant and improve the accuracy of risk estimation in COVID-19 patients.

In summary, we conclude that the C2HEST score may be a valuable tool for predicting adverse COVID-19 outcomes in hospitalized all-comers. Furthermore, the simplicity of the C2HEST score should be considered as its advantage.

Limitations

We identified several limitations in this study. First, our results are based on data from an analysis of hospitalized cases at a single center, which may affect the validity of our conclusions regarding other cohorts. Second, the data collection period was 2021-2022, i.e., before the dominance of the

Omicron variant, which has altered our understanding of the disease, its severity, and its course. Third, this study analyzed the entire cohort of COVID-19 patients, and, like other medical scales assessing the risk of morbidity and mortality, its applicability may be limited in certain circumstances, such as in a subpopulation with a specific comorbid condition. Fourth, we do not have information about the vaccination status of patients before their admission to the hospital.

Conclusions

We have demonstrated the usefulness and performance of the C2HEST score in predicting adverse COVID-19 outcomes in hospitalized individuals. The simplicity of this score, which can be calculated based on comorbidities, may meet medical needs in risk-stratifying COVID-19 patients admitted to the hospital. Early identification of individuals at high risk of developing critical illness is crucial and may facilitate appropriate management and optimize resource utilization. Consequently, it could provide an essential foundation for supporting appropriate triage of COVID-19-positive patients upon admission, followed by an adequate diagnostic and therapeutic decision.

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Data accessibility on the reasonable request.

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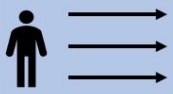
The C_2HEST score on admission to hospital may successfully predict the clinical outcomes of COVID-19 in all-comers population

MATERIAL: *2184*

Retrospective analysis II.2020-VI.2021

METHODS:



C_2HEST score:

- low risk 0-1
- medium risk 2-3
- high risk > 4

outcomes

- ❑ in-hospital mortality
- ❑ 3-month and 6-month all-cause mortality
- ❑ non-fatal endpoints
- ❑ adverse in-hospital events

RESULTS:

+1 C2HEST-point → **1.4-fold increase in risk for death**

Predictive value for:

- ❑ pneumonia
- ❑ sepsis
- ❑ cardiogenic shock
- ❑ myocardial injury
- ❑ acute heart failure
- ❑ kidney/liver injury
- ❑ stroke
- ❑ gastrointestinal bleeding

CONCLUSIONS:

The C2HEST scale can USEFULL in predicting adverse COVID-19 outcomes

Table 1. Baseline characteristics of the C2HEST risk-stratified study cohort

	Low risk [0-1]	**Medium risk [2-3]**	**High risk [>4]**	**Omnibus p-*value***	**p-*value* (for post-hoc analysis)**
variables, units (N)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)		
			Demographics		
age, years (2184)	51.1±15.9 17-74 (1418)	75.6±11.7 29-100 (492)	78.6±9.4 38-100 (274)	<0.0001	<0.0001[a, b] 0.0003[c]
≥ 65 years (2184)	376/1418 (26.5%)	419/492 (85.2%)	252/274 (92%)	<0.0001	<0.0001[a, b] 0.0259 [c]
male sex (2184)	735/1418 (51.8%)	208/492 (42.3%)	139/274 (50.7%)	0.0012	0.00095[a], 1.0[b], 0.088 [c]
BMI, kg/m2 (554)	28.3±5.1 15.4-49.4 (397)	29.3±5.6 18.6-47.8 (90)	27.8±5.8 16.4-48.2 (67)	0.210	N/A
BMI <18.5 kg/m2 (554)	3/397 (0.8%)	0/90 (0.0%)	2/67 (3.0%)	0.1882	N/A
BMI ≥30 kg/m2 (554)	132/397 (33.2%)	38/90 (42.2%)	21/67 (31.3%)	0.1882	N/A
smoking never/previous/current (2180)	(1338/1418 (94.4%) 46/1418 (3.2%) 34.1418 (2.4%)	431/489 (88.1%) 35/489 (7.2%) 23/489 (4.7%)	218/273 (79.9%) 36/273 (13.2%) 19/273 (7.0%)	<0.0001	<0.0001[a, b] , 0.0216 [c]
			Co-morbidities		
hypertension (2184)	416/1418 (29.3%)	357/492 (72.6%)	249/274 (90.9%)	<0.0001	<0.0001 [a, b, c]
DM (2182)	209/1418 (14.7%)	146/419 (29.7%)	118/273 (43.2%)	<0.0001	<0.0001 [a, b, c]
dyslipidemia (826)	289/418 (69.1%)	174/233 (74.7%)	148/175 (84.6%)	<0.0005	0.48[a], 0.0005[b], 0.064[c]
AFib/AFL (2184)	49/1418 (3.5%)	106/492 (21.5%)	135/274 (49.3%)	<0.0001	<0.0001[a, b, c]
past coronary revascularization (2184)	6/1418 (0.42%)	37/492 (7.5%)	111/274 (40.5%)	<0.0001	<0.0001[a, b, c]
past MI (2184)	11/1418 (0.8%)	63/492 (12.8%)	117/274 (42.7%)	<0.0001	<0.0001[a, b, c]
HF (2184)	0/1418 (0%)	53/492 (10.8%)	202/274 (73.7%)	<0.0001	<0.0001[a, b, c]

moderate or severe VHD/valve surgery (2184)	13/1418 (0.9%)	32/492 (6.5%)	51/274 (18.6%)	<0.0001	<0.0001[a, b, c]
PAD (2184)	26/1418 (1.8%)	31/492 (6.3%)	43/274 (15.7%)	<0.0001	<0.0001[a, b, c]
past stroke /TIA (2184)	47/1418 (3.3%)	59/492 (12.0%)	58/274 (21.2%)	<0.0001	<0.0001[a, b], 0.00312[c]
CKD (2184)	70 /1418 (4.9%)	70/492 (14.2%)	91/274 (33.2%)	<0.0001	<0.0001[a, b, c]
hemodialysis (2184)	19/1418 (1.3%)	20/492 (4.1%)	19/274 (7.0%)	<0.0001	<0.0001[a, b], 0.356 [c]
asthma (2184)	54/1418 (3.8%)	20/492 (4.1%)	11/274 (4.0%)	0.962	N/A
COPD (2184)	6/1418 (0.4%)	25/492 (5.1%)	44/274 (16.1%)	<0.0001	<0.0001[a, b, c]
hypothyroidism (2184)	76/1418 (5.4%)	68/492 (13.8%)	64/274 (23.4%)	<0.0001	<0.0001[a, b], 0.0035[c]
Hyper-thyroidism (2184)	4/1418 (0.3%)	10/492 (2.0%)	7/274 (2.6%)	<0.0001	0.0013[a], 0.0015[b], <0.0001[c]

Continuous variables are presented as mean±SD, range (minimum-maximum), and number of non-missing values. Categorized variables are presented as a percentage. Information about the numbers with valid values can be found in the left column. Abbreviations: N – valid measurements, n – number of patients with parameter above cut-off point, SD – standard deviation, BMI – body mass index, DM – diabetes mellitus, AF/AFL – atrial fibrillation/flutter, MI – myocardial infarction, HF – heart failure, PAD – peripheral artery disease, TIA – transient ischemic attack, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease, VHD – valvular heart disease, N/A – not-applicable, a – *low*- vs. *medium*-risk, b – *low*- vs. *high*-risk, c – *medium*- vs. *high*-risk

Table 3. The total all-cause and in-hospital death for C2HEST risk stratification.

	Total deaths			In-hospital deaths		
Overall	HR	95%CI	*p-value*	HR	95%CI	*p-value*
	1.40	1.346-1.453	<0.0001	1.272	1.205-1.343	<0.0001
Risk strata						
Medium- vs. *low*-risk	3.43	2.808-4.091	<0.0001	2.315	-	-
High- vs. *low*-risk	5.10	4.086-6.136	<0.0001	2.960	-	-

Abbreviations: HR – hazard ratio

Table 2. Total and in-hospital all-cause mortality in the C2HEST risk strata.

	Low risk [0-1]	**Medium risk [2-3]**	**High risk [>4]**		
Variables, units (N)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)	Mean ± SD min-max (N) or n/N (% of risk category)	Omnibus *p-value*	*p-value* (for post-hoc analysis)
All-cause mortality rate					
In-hospital (2184)	119/1418 (8.4%)	110/492 (22.4%)	97/274 (35.4%)	<0.0001	<0.0001[a, b], 0.0004 [c]
3-month (2088)	201/1343 (15%)	198/475 (41.7%)	147/270 (53.6%)	<0.0001	<0.0001[a, b], 0.0031 [c]
6-month (1117)	214/571 (37.5%)	208/331 (62.8%)	156/215 (56.9%)	<0.0001	<0.0001[a, b], 0.0713 [c]

Categorized variables are presented as a percentage. Abbreviations: N – valid measurements, n – number of patients with parameter above cut-off point, SD – standard deviation, ANOVA – analysis of variance, N/A – non-applicable, a – *low*- vs. *medium*-risk, b – *low*- vs. *high*-risk, c – *medium*- vs. *high*-risk

Table S1. Baseline characteristics of the study cohort - treatment applied before hospitalization

Variables. Units (N)	**Low risk [0-1]** n/N (% of risk category)	**Medium risk [2-3]** n/N (% of risk category)	**High risk [>4]** n/N (% of risk category)	**Omnibus** *p-value*	***p-value*** (for post-hoc analysis)
Treatment applied before hospitalization					
ACEI (2184)	116/1418 (98.2%)	120/492 (24.4%)	116/274 (42.3%)	<0.0001	<0.0001 [a. b. c]
ARB (2184)	76/1418 (5.4%)	38/492 (7.7%)	30/274 (10.9%)	0.0015	0.217 [a], 0.0024 [b], 0.51 [c]
MRA (2184)	18/1418 (1.3%)	33/492 (6.7%)	49/274 (17.9%)	<0.0001	<0.0001 [a. b. c]
SACU/VAL (2184)	6/1418 (0.4%)	3/492 (0.6%)	1/274 (0.4%)	0.888	N/A
BB (2184)	197/1418 (13.9%)	179/492 (36.4%)	157/274 (57.3%)	<0.0001	<0.0001 [a. b. c]
Cardiac glycosides (2184)	3/1418 (0.2%)	6/492 (1.2%)	10/274 (3.6%)	<0.0001	0.034 [a], <0.0001 [b], 0.099 [c]
NonDP-CCB (2184)	1/1418 (0.8%)	13/492 (2.6%)	14/274 (5.1%)	<0.000	0.0101 [a], <0.0001 [b], 0.301 [c]
DP-CCB (2184)	103/1418 (7.3%)	84/492 (17.1%)	74/274 (27.0%)	<0.0001	<0.0001 [a. b], 0.00467 [c]
AB (2184)	45/1418 (3.2%)	34/492 (6.9%)	39/274 (14.2%)	<0.0001	0.0017 [a], <0.0001 [b], 0.0044 [c]
ThD/ThLD (2184)	68/1418 (4.8%)	47/492 (9.6%)	35/274 (12.8%)	<0.000	0.0006 [a] <0.0001 [b] 0.623 [c]
LD (2184)	39/1418 (2.8%)	65/492 (13.2%)	81/274 (29.6%)	<0.0001	<0.0001 [a. b. c]
Statin (2184)	103/1418 (7.3%)	121/492 (24.6%)	126/274 (46.0%)	<0.0001	<0.0001 [a. b. c]
AA (2184)	81/1418 (5.7%)	95/492 (19.3%)	82/274 (29.9%)	<0.000	<0.0001 [a. b], 0.0034 [c]
P_2Y_{12} inhibitor (as the 2nd antiplatelet drug) (2184)	7/1418 (0.5%)	10/492 (2.0%)	22/274 (8.0%)	<0.0001	0.0228 [a], <0.0001 [b. c]
LMWH (184)	74/1418 (5.2%)	41/492 (8.3%)	26/274 (9.5%)	0.0049	0.05 [a], 0.0276 [b], 1.0 [c]
VKA (2184)	10/1418 (0.7%)	14/492 (2.8%)	23/274 (8.4%)	<0.0001	0.0018 [a], 0.0016 [b], 0.0034 [c]
NOAC (2184)	18/1418 (1.3%)	37/492 (7.5%)	52/274 (19.0%)	<0.0001	<0.0001 [a. b. c]
Insulin (2184)	62/1418 (4.4%)	29/492 (6.0%)	40/274 (14.6%)	<0.0001	0.642 [a], <0.0001 [b], 0.0003 [c]
MTF (2184)	104/1418 (7.3%)	67/492 (13.6%)	51/274 (18.6%)	<0.0001	0.00012 [a], <0.0001 [b, 0.25 [c]
SGLT2 inhibitor (2184)	11/1418 (0.8%)	7/492 (1.4%)	9/274 (3.3%)	0.0049	0.826 [a], 0.0065 [b], 0.336 [c]
ODD (other than SGLT2 inhibitor/MTF (2184)	27/1418 (1.9%)	34/492 (6.9%)	28/274 (10.2%)	<0.0001	<0.0001 [a. b], 0.424 [c]
PPI (2184)	89/1418 (6.3%)	75/492 (15.2%)	86/274 (31.4%)	<0.0001	<0.0001 [a. b. c]
Oral CCS (2184)	62/1418 (4.4%)	24/492 (4.9%)	7/274 (2.6%)	0.1819	N/A
immunosuppressive drug (other than oral CCS) (2184)	49/1418 (3.5%)	22/492 (4.5%)	2/274 (0.7%)	0.0204	1.0 [a], 0.0793 [b], 0.0254 [c]

Categorized variables are presented as a percentage. Information about the numbers with valid values can be found in the left column. Abbreviations: N – valid measurements, n – number of patients with parameters above the cut-off point. ACEI – angiotensin-converting-enzyme inhibitor, ARB – angiotensin receptor blockers. AA – acetylsalicylic acid, AB – α-adrenergic blocker, BB – β-blocker, CCS – corticosteroid, DP-CCB – dihydropyridine calcium channel blocker, LD – loop diuretic, LMWH – low molecular weight heparin, MRAs - mineralocorticoid receptor antagonist, MTF – metformin, NOAC – novel oral anticoagulants, NonDP-CCB – non-dihydropyridine calcium channel blocker, ODD – oral antidiabetic drug, PPI – proton pump inhibitor, SACU/VAL – sacubitril/valsartan, SGLT2 inhibitor – sodium glucose co-transporter-2 inhibitor, ThD/ThLD thiazide/thiazide-like diuretic, VKA – vitamin K antagonists, N/A – non-applicable, a – *low*- risk vs. *medium*-risk. b – *low*- vs. *high*-risk. c – *medium*- vs. *high*-risk

Table S2. Patient-reported symptoms and abnormalities measured on admission during physical exam

	Low risk [0-1]	**Medium risk [2-3]**	**High risk [>4]**	**Omnibus p-*value***	**p-*value* (for post-hoc analysis)**
variables, units (N)	mean±SD min-max (N) or n/N (% of risk category)	mean±SD min-max (N) or n/N (% of risk category)	mean±SD min-max (N) or n/N (% of risk category)		
		patient-reported symptoms			
cough (2184)	455/1418 (32.1%)	124/492 (25.2%)	69/274 (25.2%)	0.0035	0.0151 [a], 0.0852 [b], 1.0 [c]
dyspnea (2184)	569/1418 (40.1%)	206/492 (41.9)	146/274 (53.3%)	0.0003	1.0 [a], 0.0002 [b], 0.0091[c]
chest pain (2184)	102/1418 (7.2%)	34/492 (6.9%)	27/274 (9.9%)	0.213	N/A
hemoptysis (2184)	9/1418 (0.6%)	2/492 (0.4%)	4/274 (1.5%)	0.22	N/A
SMD (2184)	61/1418 (4.3%)	10/492 (2.0%)	5/274 (1.8%)	0.017	0.0937 [a], 0.231 [b], 1.0 c
TED (2184)	49/1418 (3.5%)	10/492 (2.0%)	7/274 (2.6%)	0.252	N/A
abdominal pain (2184)	104/1418 (7.3%)	26/492 (5.3%)	17/274 (6.2%)	0.275	N/A
diarrhea (2184)	75/1418 (5.3%)	33/492 (6.7%)	19/274 (6.9%)	0.357	N/A
nausea/vomiting (2184)	57/1418 (4.0%)	27/492 (5.5%)	14/274 (5.1%)	0.346	N/A
		Measured vital signs			
body temperature, °C (1186)	37.1+0.88 34.4 - 40.5 (810)	36.9+0.9 35.0 - 40.0 (235)	36.9+0.86 35.2 - 40.0 (141)	0.0552	N/A
heart rate, beats/minute (1672)	86.4 + 15.63 48 – 160 (1045)	84.1+16.48 50 – 160 (387)	84.8+18.79 36 – 170 (240)	0.0442	0.048 [a], 0.418 [b], 0.902 [c]
RR, breaths/minute (318)	18.4+5.78 12 – 50 (204)	18.7+5.45 12 – 45 (68)	19.3+6.09 12 – 50 (46)	0.618	N/A
SBP, mmHg (1669)	130.7+21.28 60 – 240 (1040)	134.2+25.36 50 – 270 (385)	134.5+24.7 70 – 210 (244)	0.0107	0.041 [a], 0.071 [b], 0.991 [c]
< 100 mmHg (1669)	45/1040 (4.3%)	18/385 (4.7%)	15/244 (6.15%)	0.479	N/A
DBP, mmHg (1661)	78.5+12.68 40 – 150 (1037)	78.1+13.67 40 – 157 (380)	75.8+15.3 40 – 143 (244)	0.0319	0.813 [a], 0.024 [b], 0.141 [c]
MAP, mmHg (1660)	96.0+14.25 46.7 - 179 (1037)	97.2+15.51 59.7 - 190 (379)	95.3+16.71 50 - 165.33 (244)	0.317	N/A
PP (1660)	52.3+15.3 11 - 136 (1037)	57.2+18.44 20 - 120 (379)	58.7+19.0 20 - 130 (244)	<0.0001	<0.0001 [a, b], 0.581 [c]
SpO2 on room air, % (FiO2=21%) (1263)	92.8+7.12 48 – 100 (815)	89.7+9.64 50 – 100 (281)	90.2+8.54 50 – 99 (167)	<0.0001	<0.000 [a], 0.0006 [b], 0.848 [c]
<90% (1263)	183/815 (22.5%)	102/281 (36.3%)	57/167 (34.1%)	<0.0001	<0.0001 [a,] 0.0058 [b],1.0[c]
GCS, points (884)	14.7+1.78 3.0 - 15.0 (575)	14.5+1.68 3.0 - 15.0 (191)	14.1+2.43 3.0 - 15.0 (118)	0.0645	N/A
		Abnormalities detected during physical examination			
cracles (2184)	154/1418 (10.9%)	99/492 (20.1%)	66/274 (24.1%)	<0.0001	<0.0001 [a, b], 0.704 [c]
wheezing (2184)	94//1418 (6.6%)	56/492 (11.4%)	69/274 (25.2%)	<0.0001	0.00312 [a], <0.0001 [b, c]
PC (2184)	184/1418 (13.0%)	105/492 (21.3%)	78/274 (28.5%)	<0.0001	<0.0001 [a, b], 0.0999 [c]
PO (2184)	76/1418 (5.4%)	60/492 (12.2%)	53/274 (19.3%)	<0.0001	<0.0001 [a, b] , 0.0307 [c]
VES-13, points (90)	4.1+2.86 1 – 9 (28)	5.6+3.33 1 – 12 (37)	6.5+2.89 3 – 13 (25)	0.0155	0.132 [a,] 0.013 [b], 0.552 [c]

Continuous variables are presented as: mean ± SD, range (min-max), and number of non-missing values. Categorized variables are presented as a percentage. Information about numbers with valid values can be seen in

the left column. Abbreviations: SD – standard deviation, ANOVA – analysis of variance, N – valid measurements, n – number of patients with parameter above cut-off point, GCS – Glasgow Coma Scale, DBP – diastolic blood pressure, MAP – mean blood pressure, PC – pulmonary congestion, PO – peripheral edema, PP - Pulse pressure, RR – respiratory rate, SBP – systolic blood pressure, SMD – smell dysfunction, TED – taste dysfunction, VES-13 – Vulnerable Elders Survey, N/A – not-applicable, a – *low*- vs. *medium*-risk, b – *low*- vs. *high*-risk, c – *medium*- vs. *high*-risk

Table S3. Laboratory parameters measured during hospitalization

Parameter	**assessment time**	**units**	**Low risk [0-1]** mean±SD min-max (N) or n/N (% of risk category) (N)	**Medium [2-3]** mean±SD min-max (N) or n/N (% of risk category) (N)	**High risk [>4]** mean±SD min-max (N) or n/N (% of risk category) (N)	**Omnibus *p-value***	***p-value*** **(for post-hoc analysis)**
			Complete blood count				
LEU (2050)	on admission	10^3/µl	9.0±12.34 0.51-304.02 (1302)	9.4±11.48 0.51-215.97 (480)	9.3±7.97 1.19-99.73 (268)	0.8003	N/A
		>12 x10^3/µl	202/1302 (15.5%)	84/480 (17.5%)	53/268 (19.8%)	0.4281	N/A
		4-12 x10^3/µl	971/1302 (74.6%)	345/480 (71.9%)	191/268 (71.3%)		
		<4 x10^3/µl	129/1302 (9.9%)	51/480 (10.6%)	24/268 (9%)		
	on discharge	10^3/µl	9.1±10.83 0.67-342.01 (1302)	10.6±16.33 0.44-314.44 (480)	10.1±7.18 1.19-58.49 (268)	0.0663	N/A
		>12 x10^3/µl	201/1302 (15.4%)	103/480 (21.5%)	65/268 (24.3%)	0.00046	0.007 [a], 0.006 [b] 0.927 [c]
		4-12 x10^3/µl	1017/1302 (78.1%)	337/480 (70.2%)	188/268 (70.1%)		
		<4 x10^3/µl	84/1302 (6.5%)	40/480 (8.3%)	15/268 (5.6%)		
LYMPH (1296)	on admission		1.65±10.81 0.03-296.61 (764)	1.2±1.09 0.11-12.1 (331)	1.4±5.51 0.09-78.58 (201)	0.4150	N/A
		<1 x10^3/µl	383/764 (50.1%)	175/331 (52.9%)	118/201 (58.7%)	0.2667	N/A
		1-5 10^3/µl	373/764 (48.8%)	152/331 (45.9%)	82/201 (40.8%)		
		>5 x10^3/µl	8/764 (1.0%)	4/331 (1.2%)	1/201 (0.5%)		
	on discharge	10^3/µl	1.9±4.41 0.06-114.12 (764)	1.5±1.84 0.05-26.71 (331)	1.5±4.8 0.14-66.97 (201)	0.1052	N/A
		<1 x10^3/µl	176/764 (23.0%)	113/331 (34.1%)	109/201 (54.2%)	<0.0001	0.001 [a] <0.0001[b, c]
		1-5 10^3/µl	578/764 (75.7%)	213/331 (64.4%)	89/201 (44.3%)		
		>5 x10^3/µl	10/764 (1.3%)	5/331 (1.5%)	3/201 (1.5%)		
NEUTR (1299)	on admission		6.6±5.06 0.44-53.64 (765)	6.8±4.5 0.68-33.61 (333)	7.1±5.08 0.23-29.85 (201)	0.3951	N/A
		<1.5 x10^3/µl	21/765 (2.7%)	9/333 (2.7%)	5/201 (2.5%)	0.8721	N/A
		1.5-8$10^3$/µl	550/765 (71.9%)	231/333 (69.4%)	139/201 (69.2%)		
		>8 x10^3/µl	194/765 (25.4%)	93/333 (27.9%)	57/201 (28.4%)		
	on discharge		6.6±4.81 0.22-44.09 (765)	7.5±6.09 0-41.13 (333)	7.5±4.9 0.32-23.22 (201)	0.007	0.034 [a], 0.042 [b] 1.0 [c]
		<1.5 x10^3/µl	16/765 (2.1%)	7/333 (2.1%)	3/201 (1.5%)	0.0035	0.153 [a] 0.004 [b] 1.0 [c]
		1.5-8$10^3$/µl	576/765 (75.3%)	228/333 (68.5%)	127/201 (63.2%)		
		>8 x10^3/µl	173/765 (22.6%)	98/333 (29.4%)	71/201 (35.3%)		
Hb (2050)	on admission		13.3±2.15 3.9-20.3 (1302)	12.6±2.31 4.5-18.9 (480)	12.0±2.48 5.3-18.8 (268)	<0.0001	<0.0001 [a, b], 0.003 [c]
		<12 (F), 13 (M) g/dL	346/1302 (26.6%)	195/480 (40.6%)	148/268 (55.2%)	<0.0001	<0.0001 [a, b] 0.0005 [c]
		≥12 (F), 13 (M) g/dL	956/1302 (73.4%)	285/480 (59.4%)	120/268 (44.8%)		N/A
	on discharge		12.7±2.23 5.3-18.7 (1302)	12.0±2.3 4.5-18.9 (480)	12.0±2.34 5.5-17.6 (268)	<0.0001	<0.0001 [a, b], 0.056 [c]
		<12 (F), 13 (M) g/dL	511/1302 (39.2%)	258/480 (53.8%)	172/268 (64.2%)	<0.0001	<0.0001 [a, b] 0.021 [c]
		≥12 (F), 13 (M) g/dL	791/1302 (60.8%)	222/480 (46.3%)	96/268 (35.8%)		N/A
MCV (2050)	on admission	fl	89.4 ±5.68 61.8-131.1 (1302)	89.8±6.89 60.5-124.8 (480)	90.6±6.91 62.5-116.2 (268)	0.0185	0.354 [a], 0.022 [b] 0.363 [c]
	on discharge		90.1±5.6	91.0±6.77	91.2±6.07	0.0031	0.027 [a]

			61.8-120.6 (1302)	68.4-123.1 (480)	70.7-95.0 (268)		0.023 [b], 0.933 [c]
MCH (2050)	on admission	pg	30.0±2.25 16.5-46.6 (1302)	30.0±2.88 30.1-43.5 (480)	30.0±2.76 18.1-39.8 (268)	0.865	N/A
	on discharge		29.9±2.08 16.5-37.3 (1302)	29.9±2.59 19.0-40.7 (480)	29.7±2.41 20.1-35.1 (268)	0.432	N/A
MCHC (2050)	on admission	g/dL	33.6±1.42 24.6-39.9 (1302)	33.3±1.72 24.7-38.7 (480)	33.0±1.66 27.5-38.8 (268)	<0.0001	0.005 [a], <0.0001[b] 0.108 [c]
	on discharge		33.2±1.46 24.9-39.9 (1302)	32.8±1.66 27.4-40.0 (480)	32.6±1.42 27.2-36.6 (268)	<0.0001	<0.0001[a. b] 0.061 [c]
RETICU (195)	on admission	x 10^9/L	59.7±33.69 5.3-137.6 (103)	55.7±34.67 10.1-224.4 (63)	59.5±35.37 4.5-142.3 (29)	0.758	N/A
	on discharge		61.3±33.47 4.9-137.6 (103)	58.4±40.60 7.0-230.3 (63)	55.9±35.82 9.1-162.4 (29)	0.733	N/A
PLT (2050)	on admission	x10^3/µl	235.9±108.85 0-1356 (1302)	230.1±113.91 3-740 (480)	216.8±93.38 8-578 (268)	0.0126	0.598 [a], 0.009 [b] 0.2 [c]
		>450	52/1302 (4.0%)	24/480 (5.0%)	7/268 (2.6%)	0.125	N/A
		400-450	37/1302 (2.8%)	11/480 (2.3%)	5/268 (1.9%)		
		150-400	992/1302 (76.2%)	343/480 (71.5%)	195/268 (72.8%)		
		100-150	172/1302 (13.2%)	70/480 (14.6%)	41/268 (15.3%)		
		50-100	38/1302 (2.9%)	26/480 (5.4%)	15/268 (5.6%)		
		20-50	6/1302 (0.5%)	3/480 (0.6%)	3/268 (1.1%)		
		<20	5/1302 (0.4%)	3/480 (0.6%)	2/268 (0.7%)		
	on discharge	x10^3 /µl	270.9±128.32 2-1101 (1300)	245.3±121.2 3-694 (480)	231.4±98.27 4-268.25 (268)	<0.0001	<0.0001[a. b. c]
		>450	124/1300 (9.5%)	30/480 (6.3%)	3/268 (1.1%)	<0.0001	0.0127 [a], <0.0001[b] 0.0243 [c]
		400-450	72/1300 (5.5%)	20/480 (4.2%)	8/268 (3.0%)		
		150-<400	923/1300 (71.0%)	335/480 (69.8%)	185/268 (69.0%)		
		100-150	117/1300 (9.0%)	51/480 (10.6%)	42/268 (15.7%)		
		50-100	39/1300 (3.0%)	31/480 (6.5%)	22/268 (8.2%)		
(2048)		20-50	20/1300 (1.5%)	9/480 (1.9%)	5/268 (1.9%)		
		<20	5/1300 (0.4%)	4/480 (0.8%)	3/268 (1.1%)		
Acid-base balance in the arterial blood gas							
Ph (276)	on admission		7.4±0.08 7.04-7.58 (121)	7.4±0.07 7.1-7.54 (88)	7.4±0.08 7.1-7.54 (67)	0.27	N/A
		<7.35	14/121 (11.6%)	7/88 (8.0%)	10/67 (14.9%)	0.391	N/A
		≥7.35	107/121 (88.4%)	81/88 (92.0%)	57/67 (85.0%)		
	on discharge		7.4±0.08 7.06-7.5 (121)	7.4±0.08 7.01-7.6 (88)	7.4±0.06 7.3-7.6 (67)	0.889	N/A
		<7.35	12/121 (9.9%)	9/88 (10.2%)	4/67 (6.0%)	0.597	N/A
		≥7.35	109/121 (90.1%)	79/88 (89.8%)	63/67 (94.0%)		
PaO2 (276)	on admission	<60 mmHg	38/121 (31.4%)	33/88 (37.5%)	30/67 (44.8%)	0.186	N/A
		≥60 mmHg	83/121 (68.6%)	55/88 (62.5%)	37/67 (55.2%)		
			72.2±27.29 12.8-100 (121)	76.3±47.63 28.3-100 (88)	70.6±34.56 23.7-100 (67)	0.679	N/A
	on discharge	<60 mmHg	29/121 (24.0%)	30/88 (34.1%)	32/67 (47.8%)	0.0039	0.441 [a], 0.0045 [b] 0.359 [c]
		≥60 mmHg	92/121 (76.0%)	58/88 (65.9%)	35/67 (32.2%)		
			75.4±26.57 12.8-100 (121)	77.7±48.53 23.3-100 (88)	66.4±24.15 28.5-100 (67)	0.040	0.914 [a], 0.054 [b] 0.147 [c]
PaCO2 (276)	on admission	≥ 45 mmHg	23/121 (19.0%)	10/88 (11.4%)	12/67 (17.9%)	0.309	N/A
		< 45 mmHg	98/121 (81.0%)	78/88 (88.6%)	55/67 (82.1%)		
			38.0±10.27 20.2-82.4	36.7±9.42 20.9-79.4	38.6±10.93 19.7-88.4	0.434	N/A

			(121)	(88)	(67)		
	on discharge	≥ 45 mmHg	20/121 (16.5%)	11/88 (12.5%)	10/67 (14.9%)	0.721	N/A
		< 45 mmHg	101/121 (83.5%)	77/88 (87.5%)	57/67 (85.1%)		
			38.4±9.81 20.2-75.5 (121)	37.9±10.96 20.9-88.4 (88)	38.7±10.13 25.0 – 88.4 (67)	0.896	N/A
PaO2 and PaCO2 (276)	on admission	<60 and ≥ 45 mmHg.	7/121 (5.8%)	6/88 (6.8%)	9/67 (13.4%)	0.159	N/A
		≥60 and <45 mmHg	114/121 (94.2%)	82/88 (93.2%)	58/67 (86.6%)		
	on discharge	<60 and ≥ 45 mmHg.	4/121 (3.3%)	4/88 (4.5%)	6/67 (9.0%)	0.228	N/A
		≥60 and <45 mmHg	117/121 (96.7%)	84/88 (95.5%)	61/67 (91.0%)		
HCO3-*standard* (272)	on admission	mmol/L	24.9±3.76 12.1-32.9 (120)	24.2±4.19 14.3-39.5 (85)	24.2±4.57 13.5-38.6 (67)	0.427	N/A
	on discharge		25.0±3.80 12.1-35.7 (120)	25.3±5.58 13.7-51.7 (85)	24.9±4.0 17.4-36.7 (67)	0.868	N/A
BE (108)	on admission		0.9±4.77 (-)15.7–10.5 (41)	1.7±5.30 (-)12.5-15.7 (43)	2.0±5.1.7 (-)7.4–14.6 (24)	0.642	N/A
	on discharge		0.80±5.44 (-)15.7–11.9 (41)	2.4±6.01 (-)14.7–17.1 (43)	1.4 ±4.79 (-)4.7–13.2 (24)	0.437	N/A
LACT (245)	on admission		2.5±1.60 0.6-12.8 (105)	2.0±0.86 0.5-5.7 (79)	2.5±1.82 0.6-12.0 (61)	0.021	0.047 [a], 0.977 [b] 0.128 [c]
	on discharge		2.5±1.58 0.7-12.9 (105)	2.10±1.03 0.5-6.4 (79)	2.4±1.21 0.8-6.0 (61)	0.098	N/A
LA (245)		pH <7.35 and LACT >1.6 mol/L	9/105 (8.6%)	5/79 (6.3%)	8/61 (13.1%)	0.372	N/A
		pH >7.35 or/and LACT <1.6 mol/L	96/105 (91.4%)	74/79 (93.7%)	53/61 (86.9%)		N/A
Osmolarity (203)	on admission	mOsm	303.6 ±16.72 247-370 (127)	306.1±26.04 233-373 (43)	306.4 ± 25.70 245.8- 370.6 (33)	0.725	N/A
	on discharge		299.9±16.61 270-362 (127)	303.9±22.13 263-373 (43)	305.2±23.0 265-353 (33)	0.312	N/A
Electrolytes, inflammatory and iron biomarkers							
Na (2032)	on admission	mmol/L	138.3±4.36 106-159 (1289)	137.7±7.0 101-175 (475)	137.9±6.82 108-174 (268)	0.267	N/A
	on discharge		139.1±4.30 109-175 (1289)	139.1±7.28 101-172 (475)	140.2±6.68 120-172 (268)	0.026	0.983 [a], 0.019 [b] 0.098 [c]
K (2039)	on admission	mmol/L	4.1±0.58 2.0-7.5 (1294)	4.1±0.7 2.4-7.03 (477)	4.3±0.82 2.5-8.7 (268)	<0.0001	0.104 [a], <0.0001[b] 0.025 [c]
	on discharge		4.2±0.59 2.0-7.4 (1294)	4.4±0.76 2.3-7.0 (477)	4.4±0.7 2.5-6.6 (268)	<0.0001	0.004 [a], <0.0001[b] 0.334 [c]
Mg (1483)	on admission	mg/dL	2.1±0.35 0.9-5.2 (927)	2.1±0.44 1.3-4.1 (346)	2.0±0.41 1.1-4.0 (210)	0.402	N/A
	on discharge		2.0±0.33 0.8-5.2 (927)	2.0±0.44 1.1-4.2 (346)	2.0±0.4 1.0-4.0 (210)	0.468	N/A
Cl (665)	on admission	mg/dL	103.1±5.45 80-121	102.3±6.91 66-127 (155)	103.1±8.89 79-140 (96)	0.469	N/A
	on discharge		102.7±5.26	102.4±6.97	104.4±8.37	0.127	N/A

			80-128 (414)	66-127 (155)	76-135 (96)		
CRP (2020)	on admission	mg/L	76.6±84.58 0.13-531.6 (1275)	83.2±86.63 0.3-538.6 (477)	76.5±81.18 0.4-390.9 (268)	0.341	N/A
	on discharge		48.3±79.16 0.13-497 (1275)	72.6±94.48 0.22-538.6 (477)	74.4±86.84 0.4-431.9 (268)	<0.0001	<0.0001[a.b], 0.961 [c]
Procalcitonin (1275)	on admission	ng/mL	0.8±4.48 0.01-61.3 (919)	1.8±12.02 0.01-196.0 (344)	1.5±6.09 0.01-60.8 (212)	0.136	N/A
	on discharge		0.9±5.08 0.01-75.2 (919)	1.6±6.33 0.01-81.1 (344)	1.2±5.0 0.01-60.8 (212)	0.178	N/A
IL-6 (702)	on admission	pg/mL	61.3±424.31 2-9099 (480)	43.2±63.64 2-499 (143)	64.0±96.14 2-421 (79)	0.179	N/A
	on discharge		61.3±433.58 2-9099 (480)	40.0±74.16 2-499 (143)	76.6±159.21 2-1000 (79)	0.112	N/A
ESR (133)	on admission	mm/h	39.2±34.13 2-139 (67)	30.3±25.47 1-100 (39)	43.5±33.18 3-128 (27)	0.152	N/A
	on discharge		35.4±31.18 1-139 (67)	31.3±26.48 1-100 (39)	44.6±31.04 5-126 (27)	0.202	N/A
d-dimer (1579)	on admission	µg/L	3.7±12.19 0.15-132.8 (1002)	6.5±16.76 0.2-127.2 (373)	5.4±17.25 0.22-128.0 (204)	0.00951	0.01 [a], 0.387 [b] 0.741 [c]
	on discharge		3.2±10.74 0.15-128.0 (1002)	5.6±13.29 0.21-106.02 (373)	3.7±9.24 0.21-107.54 (204)	0.00707	0.005 [a,] 0.8 [b] 0.095 [c]
PT (1925)	on admission	%	87.8±19.09 7-148 (1227)	79.7±21.3 7-131 (446)	71.5±26.47 2-124 (252)	<0.0001	<0.0001 [a. b. c]
	on discharge		87.9±19.25 7-148 (1227)	79.5±20.0 4-126 (446)	74.3±23.0 2-131 (252)	<0.0001	<0.0001[a. b] 0.008 [c]
INR (1925)	on admission	>1.5	41/1228 (3.3%)	46/445 (10.3%)	56/252 (22.2%)	<0.0001	<0.0001 [a. b. c]
		≤1.5	1187/1228 (96.7%)	399/445 (89.7%)	196/252 (77.8%)		
			1.1±0.48 0.82-15.2 (1228)	1.3±0.6 0.87-7.8 (445)	1.8±2.44 0.89-21.1 (252)	<0.0001	<0.0001[a. b. c]
	on discharge	>1.5	49/1228 (4.0%)	40/445 (9.0%)	4/252 (17.5%)	<0.0001	<0.0001 [a. b]
		≤1.5	1179/1228 (96.0%)	405/445 (91.0%)	208/252 (82.5%)		0.0044 [c]
		≤1.5	1.1±0.39 0.82-9.2 (1228)	1.27±0.76 0.88-13.1 (445)	1.4±1.44 0.87-21.1 (252)	<0.0001	0.002 [a. b] 0.154 [c]
aPTT (1868)	on admission		34.4±14.8 15.2-250.4 (1192)	33.5±10.0 16.8-150.1 (431)	39.2±22.7 17.2-250.7 (245)	0.001	0.355 [a], 0.005 [b] 0.00074 [c]
		>60 s	28/1192 (2.3%)	7/431 (1.6%)	11/245 (4.5%)	0.0634	N/A
		≤60 s	1164/1192 (97.7%)	424/431 (98.4%)	234/245 (95.5%)		
	on discharge		35.7±17.5 16.6-283.2 (1192)	35.1±11.2 16.6-138.8 (431)	38.7±20.9 17.2-230.5 (245)	0.0453	0.732 [a], 0.087 [b] 0.035 [c]
		>60 s	46/1192 (3.8%)	8/431 (1.9%)	12/245 (4.9%)	0.0718	N/A
		≤60 s	1146/1192 (96.1%)	423/431 (98.1%)	233/245 (95.1%)		
Fibrinogen (420)	on admission	g/dl	4.9±1.85 0.35-10 (285)	4.7±1.82 0.35-9.2 (81)	4.5±1.66 1.78-9.1 (54)	0.316	N/A
	on discharge		4.7±1.96 0.44-10 (285)	5.0±2.22 0.35-11.3 (81)	4.9±1.94 1.53-9.04 (54)	0.659	N/A
Ferritin (969)	on admission	ng/ml	964.7±1732.2 8-37400 (625)	806.9±965.38 8-7316 (218)	764.9±863.78 15.7-5910 (126)	0.146	N/A
	on discharge		915.2±1824.14 8-37400 (625)	808.3±1029.8 8-7970 (218)	2064.6±10327.03 17-103000 (126)	0.245	N/A
Tsat (174)	on admission	%	25.3±23.65 2.38-200 (88)	20.6±15.71 0-68.3 (50)	22.03±15.3 0-61.7 (36)	0.377	N/A
	on discharge		24.5±15.9	21.8±16.16	20.1±13.92	0.3	N/A

			3.1-86.9 (88)	0-68.3 (50)	0-50.2 (36)		
Fe (262)	on admission		55.7±39.58 10-178 (127)	46.6±38.73 10-197 (77)	49.07±44.1 10-314 (58)	0.251	N/A
	on discharge		58.6±47.49 10-366 (127)	47.1±37.95 10-197 (77)	48.6±45.31 5-320 (58)	0.137	N/A
sTfR (49)	on admission	mg/L	1.6±1.1 0.4-5.2 (17)	1.4±0.62 0.79-2.94 (20)	1.7±0.89 0.94-4.0 (12)	0.594	N/A
	on discharge		1.6±1.1 0.4-5.2 (17)	1.4±0.6 0.79-2.94 (20)	1.7±0.89 0.94-4.0 (12)	0.544	N/A
Vit. B12 (278)	on admission	pg/ml	742±1084.22 131-6000 (127)	563.4±755.85 109-5907 (82)	580.5±622.9 109-4344 (69)	0.315	N/A
	on discharge		703.8±912.66 1131-6000 (127)	635.0±764.43 109-5907 (82)	614.6±611.6 109-4344 (69)	0.705	N/A
FA (278)	on admission	ng/L	7.3±4.6 1.5-24 (125)	7.7±5.27 1.8-24 (81)	7.7±6.0 1-24 (72)	0.797	N/A
	on discharge		7.5±4.68 1.6-24 (125)	8.3±5.64 1.38-24 (81)	8.9±6.6 1-24 (72)	0.226	N/A
				Biochemistry			
Glucose (1760)	on admission	mg/dL	134.9±74.88 28-933 (1064)	151.1±92.0 47-1026 (449)	150.7±98.49 37-1064 (247)	0.00084	0.003 [a], 0.049 [b] 0.998 [c]
	on discharge		124.0±70.64 37-1444 (1064)	142.5±83.16 47-596 (449)	144.2±77.3 14-685 (247)	<0.0001	0.0001[a], 0.00057 [b] 0.961 [c]
HbA1c (263)	on admission	%	7.6±2.31 4.2-14.9 (127)	7.5±2.19 4.8-16.6 (75)	7.3±1.77 5.1-13.7 (61)	0.505	N/A
	on discharge		7.5±2.22 4.2-14.9 (127)	7.5±2.19 4.7-16.8 (75)	7.3±1.78 5.1-13.7 (61)	0.744	N/A
Urea (1859)	on admission	mg/dL	42.9±36.0 5-307 (1146)	64.4±49.48 8-353 (455)	77.2-53.6 12-369 (258)	<0.0001	<0.0001[a. b] 0.005 [c]
	on discharge		40.9±31.89 5-307 (1146)	66.3±54.16 10-396 (455)	78.2±52.16 15-342 (258)	<0.0001	<0.0001 [a. b] 0.011 [c]
Creatinine (1963)	on admission		1.15±1.18 0.26-14.87 (1217)	1.45±1.3 0.48-12.66 (478)	1.8±1.58 0.44-11.3 (268)	<0.0001	<0.0001 [a. b] 0.005 [c]
		≥5 mg/dL	23/1217 (1.9%)	17/478 (3.6%)	12/268 (4.5%)	<0.0001	<0.0001 [a.b] 0.00043 [c]
		>2.0 mg/dL	84/1217 (6.9%)	68/478 (14.2%)	69/268 (25.7%)		
		< 2.0	1133/1217 (93.1%)	410/478 (85.8%)	199/268 (74.3%)		
	on discharge		1.08±1.05 0.26-14.87 (1217)	1.43±1.36 0.43-12.35 (478)	1.66±1.42 0.43-7.27 (268)	<0.0001	<0.0001[a. b] 0.09 [c]
		≥5 mg/dL	19/1217 (1.6%)	14/478 (2.9%)	11/268 (4.1%)	<0.0001	<0.0001 [a. b] 0.162 [c]
		>2.0 mg/dL	76/1217 (6.2%)	72/478 (15.1%)	56/268 (20.9%)		
		< 2.0	1141/1217 (93.8%)	406/478 (84.9%)	212/268 (79.1%)		
eGFR (1958)	on admission	ml/min/ 1.73 m^2	85.0±34.34 0-433 (1212)	62.0±28.76 4-149 (478)	52.8±29.72 5-180 (268)	<0.0001	<0.0001[a. b] 0.0001 [c]
		<60	236/1212 (19.5%)	214/478 (44.8%)	166/268 (61.9%)	<0.0001	<0.0001[a. b. c]
		≥60	975/1212 (80.5%)	264/478 (55.2%)	102/268 (38.1%)		
	on discharge		89.3±34.71 0-433 (1212)	65.4±31.0 4-208 (478)	58.4±33.07 5-209 (268)	<0.0001	<0.0001 [a. b. c]
		<60	189/1212 (15.6%)	188/478 (39.3%)	145/268 (54.1%)	<0.0001	<0.0001[a. b] 0.0004 [c]
		≥60	1023/1212 (84.4%)	290/478 (60.7%)	123/268 (45.9%)		
TP (1958)	on admission	g/L	6.1±0.84 3.5-8.2 (332)	5.9±0.92 3.6-9.5 (152)	5.7±0.87 3.3-8.2 (123)	<0.0001	0.344 [a], 0.002 [b] 0.165 [c]
	on discharge		6.0±0.87	5.8±0.91	5.6±0.9	<0.0001	0.09 [a]

			3-8.2 (332)	3.7-9.1 (152)	3.3-8.1 (123)		<0.0001[b], 0.07 [c]
Albumin (665)	on admission	g/L	3.2±0.6 1.5-5.1 (375)	3.1±0.55 1.1-4.4 (160)	3.0±0.61 0.7-4.9 (130)	0.00652	0.488 [a], 0.005 [b] 0.123 [c]
	on discharge		3.1±0.67 0.4-5.1 (375)	3.0±0.56 1.7-4.4 (160)	2.8±0.61 0.9-4.5 (130)	0.0009	0.632 [a], 0.00059 [b] 0.019 [c]
UA (623)	on admission	mg/dL	5.5±2.54 1.4-23.6 (348)	6.5±3.0 1.7-18.4 (160)	6.6±2.44 1.7-13.6 (115)	<0.0001	0.0008 [a], 0.0001 [b] 0.934 [c]
	on discharge		5.2±2.28 1.1±20.4 (348)	6.2±3.03 1.9-18.6 (160)	6.3±2.32 1.7-13.2 (115)	<0.0001	0.001 [a], 0.0001 [b] 0.97 [c]
AST (1443)	on admission	IU/L	60.1±113.94 5-2405 (884)	66.5±258.19 7-4776 (347)	86.1±324.26 8-3866 (212)	0.477	N/A
	on discharge		92.2±842.08 5-23896 (884)	71.8±360.57 8-6591 (347)	122.4±568.21 7-6088 (212)	0.485	N/A
ALT (1590)	on admission	IU/L	54.9±92.79 4-1411 (973)	49.0±190.0 4-3700(391)	51.7±143.3 5-1361 (226)	0.813	N/A
	on discharge		70.4±193.78 4-5163 (973)	50.2±90.43 5-1247 (391)	72.7±261.64 5-2985 (226)	0.0229	0.024 [a],0.992 [b] 0.425 [c]
ALP (829)	on admission	U/L	94.2±109.9 22-1503 (503)	81.3±71.0 28-723 (194)	91.9±73.9 13-500 (129)	0.169	N/A
	on discharge		94.0±111.0 22-1467 (503)	81.6±56.82 28-526 (194)	91.8±63.51 28-417 (129)	0.113	N/A
GGTP (1352)	on admission	U/L	91.7±161.74 6-2532 (828)	74.6±105.73 8-975 (333)	73.0±108.17 9-687 (191)	0.0538	N/A
	on discharge		95.1±136.28 6-1771 (828)	82.4±120.44 7-1091 (333)	76.1±115.87 6-1207 (191)	0.0843	N/A
LDH (1232)	on admission	U/L	430.0±378.19 50-7100 (776)	391.3±201.86 44-1357 (286)	441.3±733.17 71-9505 (170)	0.0869	N/A
	on discharge		388.4±566.69 50-11227 (776)	370.6±207.76 44-1584 (286)	457.7±814.13 97-9505 (170)	0.327	N/A
Cardiac biomarkers							
BNP (359)	on admission	pg/ml	220.0±638.68 1.7-6924.2 (161)	444.4±808.15 3-4890.6 (100)	1020.7±239.36 5.9-13368.4 (98)	0.0002	0.051 [a], 0.0008 [b] 0.028 [c]
	on discharge		219.0±368.79 1.7-6924.2 (161)	466.2±1206.0 3-10662.8(100)	933.8±1911.84 11.9-13368.4 (98)	0.000716	0.145 [a,] 0.001 [b] 0.103 [c]
NT-proBNP (379)	on admission	ng/ml	1888.8±7779.04 12-70000 (172)	8483.2±14594.98 18.2-70000 (109)	14121.7±19061.73 119.6-70000 (98)	<0.0001	<0.0001[a, b] 0.049 [c]
	on discharge		1821.5±6819.5 12-70000 (172)	9269.8±15684.9 18.2-70000 (109)	13186.2±17523.6 119.6-70000 (98)	<0.0001	<0.0001[a, b] 0.213 [c]
Troponin T (1176) (F ≤ 15.6 M ≤ 34.2)	on admission	pg/ml	136.6±807.93 0-11758.2 (678)	1706.7±1163.78 1-125593 (305)	761.7±2633.94 3.3-21022.9 (191)	0.00043	0.05 [a], 0.004 [b] 0.361 [c]
		≤5-fold upper range	611/678 (90.1%)	239/305 (78.4%)	138/191 (72.3%)	<0.0001	<0.0001 [a, b] 0.448 [c]
		>5-fold upper range	67/678 (9.9%)	66/305 (21.6%)	53/191 (27.7%)		
	on discharge		116.9±827.21 0.2-12391.6 (678)	1864.3±1329.37 0.8-174653 (305)	662.9±2784.48 1.8-29828.3 (191)	0.00237	0.058 [a], 0.022 [b] 0.28 [c]
	during hospitali-zation	≤5-fold upper limit	588/678 (86.7%)	232/305 (76.1%)	129/191 (67.5%)	<0.0001	0.0001 [a], <0.000 [b] 0.146 [c]
		>5-fold upper limit	90/678 (13.3%)	73/305 (23.9%)	62/191 (32.5%)		
cLDL (456)	on admission		99.8±50.97 6-510 (233)	87.2±40.59 17-230 (129)	74.8±42.29 6-210 (88)	<0.0001	0.028 [a], <0.0001[b] 0.085 [c]

		>115 mg/dL	74/233 (31.8%)	30/129 (23.3%)	14/88 (15.9%)	0.0105	0.335 [a], 0.0208 [b]
		≤115 mg/dL	159/233 (68.2%)	97/129 (76.7%)	74/88 (84.1%)		0.751 [c]
cHDL (452)	on admission	mg/dl	39.9±16.1 2-120 (237)	40.2±15.37 7-110 (129)	37.2±15.0 8-79 (86)	0.306	N/A
TG (641)	on admission		178.9±123.96 40-1100 (360)	144.5±96.41 48-595 (164)	129.6±61.6 46-413 (117)	<0.0001	0.002 [a], <0.0001[b] 0.258 [c]
		>150 mg/dL	177/360 (49.2%)	50/164 (30.5%)	37/117 (31.6%)	<0.0001	0.0003 [a], 0.004 [b]
		≤150 mg/dL	183/360 (50.8%)	114/164 (69.5%)	80/117 (68.4%)		1.0 [c]
Hormones							
25-OH-vit.D (474)	on admission	ng/mL	24.7±17.57 3.5-146.1 (305)	24.8±16.5 3.5-77.7 (108)	19.2±14.72 3.5-63.5 (61)	0.0296	0.999 [a], 0.029 [b] 0. 063 [c]
TSH (820)	on admission	mIU/L	1.3±1.54 0-18.6 (441)	1.6±2.46 0.01-28.81 (232)	2.2±3.96 0-38.24 (147)	0.02904	0.47 [a], 0.035 [b] 0.197 [c]
fT4 (339)	on admission	pmol/L	12.7±2.91 6.68-33.47 (184)	12.8±3.39 5.92-36.6 (92)	13.4±4.06 7.87-35.46 (63)	0.430	N/A
fT3 (315)	on admission	pmol/L	2.3±1.89 0.95-25.25 (177)	1.85±0.76 0.95-4.45 (84)	1.76±1.02 0.95-6.85 (54)	0.015	0.01 [a], 0.156 [b] 0.755 [c]
ACTH (10)	on admission		12.0±11.58 5-32.2 (5)	19.4±4.21 16.5-24.2 (3)	19.2±10.96 11.4-26.9 (2)	0.589	N/A
Cortisol (120)	on admission	µg/dL	13.5±16.11 0.1-119.6 (80)	15.0±13.46 1-59.8 (23)	12.4±7.83 0.9-29.6 (17)	0.743	N/A

Continuous variables are presented as: mean ± SD. range (minimum -maximum) and number of non-missing values. Categorized variables are presented as: a number with a percentage. Information about the numbers with valid values is provided in the left column. Abbreviations: N-valid measurements. n - number of patients with parameter above cut-off point. SD - standard deviation, FA – folic acid, Hb – hemoglobin, HbA1c – glycated hemoglobin, LA – lactate acidosis, LACT – lactates, LEU – leucocytes, LYMPH – lymphocytes, MCV – mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, NEUTR – neutrophils, PLT – platelets, PT – prothrombi**n** rate, RETICU – reticulocytes**,** UA – uric acid, TP – total protein, N/A – non-applicable. a – *low*- vs. *medium*-risk, b – *low*- vs. *high*-risk, c – *medium*- vs. *high*-risk

Table S4. Therapies used during hospitalization

variables. Units (N)	Low risk [0-1]	Medium risk [2-3]	High risk [>4]	Omnibus *p-value*	*p-value* (for post-hoc analysis)
	n/N (% of risk category)	n/N (% of risk category)	n/N (% of risk category)		
Applied treatment and procedures					
systemic CCS (2184)	708/1418 (49.9%)	246/492 (50.0%)	142/274 (51.8%)	0.844	N/A
Convalescent plasma (2184)	167/1418 (11.8%)	41/492 (8.3%)	31/274 (11.3%)	0.106	N/A
TCZB (2184)	22/1418 (1.6%)	2/492 (0.4%)	1/274 (0.4%)	0.063	N/A
RDV (2184)	236/1418 (16.6%)	72/492 (14.6%)	356/274 (12.8%)	0.208	N/A
Antibiotic (2184)	747/1418 (52.7%)	303/492 (61.6%)	191/274 (69.7%)	<0.0001	0.0023 [a], <0.0001[b] 0.0893 [c]

Categorized variables are presented as: a number with a percentage. Information regarging the numbers with valid values is provided in the left column.

Abbreviations: N-valid measurements. n - number of patients with parameters above cut-off point. SD – standard deviation. N/A – non-applicable, CCS – corticosteroid, TCZB – tocilizumab, RDV – remdesivir, a – *low*- vs. *medium*-risk, b – *low*- vs. *high*-risk, c – *medium*- vs. *high*-risk

Table S5. Applied treatment and procedures.

	Low risk [0-1]	**Medium risk [2-3]**	**High risk [>4]**	**Omnibus *p-value***	***p-value* (for post-hoc analysis)**
variables, units (N)	mean±SD min-max (N) or n/N (% of risk category)	mean±SD min-max (N) or n/N (% of risk category)	mean±SD min-max (N) or n/N (% of risk category)		
Applied treatment and procedures					
The most ARS during hospitalization (2181)					
• no oxygen	742/1416 (52.4%)	202/491 (41.1%)	89/274 (32.5%)	<0.0001	<0.0001[a, b] 0.212 [c]
• high-flow nasal cannula (non-invasive ventilation)	65/1416 (4.6%)	39/491 (7.9%)	27/274 (9.9%)		
• invasive ventilation	141/1416 (10.0%)	49/491 (10.0%)	22/274 (8.0%)		
Oxygenation parameters from the qualification period for ARS:	90.6±7.9	86.5±9.7	85.6±9.96		<0.0001[a, b]
• SpO2 (632)	50 – 100 (411)	55 – 99 (133)	59 – 99 (88)	<0.0001	0.78 [c]
• RR, breaths/minute (105)	26.5±8.5 14 – 50 (55)	29.7±13.9 13 – 66 (28)	29.5±12.87 14 – 72 (22)	0.3799	N/A
Duration of MV, days (1389)	2.1±7.65 0 – 91 (925)	1.4±5.19 0 – 51 (296)	1.2±4.12 0 – 29 (168)	0.051	N/A
Therapy with CA (2184)	131/1418 (9.2%)	45/492 (9.1%)	42/274 (15.3%)	0.0068	1.0 [a], 0.0099 [b], 0.041 [c]
Coronary angiography (2184)	10/1418 (0.7%)	12/492 (2.4)	8/274 (2.9)	0.00092	<0.0148[a],<0.0127[b] 1.0[c]
Coronary revascularization (2184)	8/1418 (0.6%)	11/492 (2.2%)	7/274 (2.6%)	0.00069	<0.0085[a],<0.0162[b] 1.0[c]
Hemodialysis (2184)	47/1418 (3.3%)	12/492 (2.6%)	12/274 (4.4%)	0.434	N/A

Continuous variables are presented as mean ± SD, range (min-max), and non-missing values. Categorized variables are presented as a percentage. Information about the numbers with valid values is provided in the left column.

Abbreviations: N – valid measurements, n – number of patients with parameter above cut-off point, SD – standard deviation, ANOVA – analysis of variance, ARS – advanced respiratory support, CA – catecholamines MV – mechanical ventilation, RR – respiratory rate, N/A – non-applicable, a – *low*- vs. *medium*-risk, b – *low*- vs. *high*-risk, c – *medium*- vs. *high*-risk

Table S6. The Log-rank statistics for best matching the C2HEST risk strata for a total mortality.

	h2	h3	**h4**	h5	h6	h7	h8
m1	293.6412	262.6541	248.5854	218.7096	185.0598	174.1676	13.13543
m2		288.5471	**300.8929**	295.2091	283.35	281.2464	16.7678
m3			224.9257	221.4446	213.1684	212.2898	14.57013
m4				156.288	155.0826	155.259	12.44789
m5					92.64759	92.03033	9.556165
m6						29.7152	5.43322
m7							2.190821

m-*medium*. h-*high*, bold text – statistically significant values

Table S7. The Log-rank statistics for the best matching the C2HEST risk strata for a in-hospital mortality.

	h2	h3	h4	h5	h6	h7	h8
m1	76.14871	73.07586	62.72731	54.0316	41.54258	34.21328	5.393144
m2		83.28625	**86.20881**	85.94467	81.30488	78.90106	8.726322
m3			74.88727	76.14353	73.52639	72.42844	8.393051
m4				54.07173	53.20158	53.21931	7.21509
m5					37.01716	37.47576	6.072637
m6						18.82582	4.28475
m7							2.635721

m-*medium*, h-*high*, bold text – satistically significant values

Table S8. Odds ratios for quantifying the strength of the association between CH2EST-score and study endpoints and adverse events.

Endpoint	**Comparison**	**OR**	**CI min.**	**CI max.**	**P-*value***
End of hospitalization - death	overall	1.502	1.408	1.603	< 0.0001
	low vs medium	3.143	2.367	4.173	< 0.0001
	low vs high	5.982	4.383	8.164	< 0.0001
End of hospitalization – deterioration	overall	1.160	1.081	1.242	< 0.0001
	low vs medium	2.260	1.700	2.994	< 0.0001
	low vs high	1.760	1.209	2.522	0.0025
End of hospitalization - rehabilitation	overall	1.005	0.928	1.084	0.9067
	low vs medium	1.140	0.834	1.543	0.4017
	low vs high	0.921	0.600	1.371	0.6956
End of hospitalization – full recovery	overall	0.712	0.673	0.752	< 0.0001
	low vs medium	0.346	0.280	0.427	< 0.0001
	low vs high	0.258	0.196	0.337	< 0.0001
Shock – all-cause	overall	1.137	1.046	1.233	0.0022
	low vs medium	1.239	0.856	1.766	0.2453
	low vs high	1.644	1.074	2.459	0.0182
Cardiogenic shock	overall	1.632	1.384	1.928	< 0.0001
	low vs medium	4.610	1.805	12.590	0.0017
	low vs high	10.854	4.471	28.878	< 0.0001
Septic shock	overall	1.088	0.986	1.196	0.0848
	low vs medium	0.970	0.623	1.469	0.8875
	low vs high	1.304	0.784	2.081	0.2846
PE	overall	1.041	0.932	1.155	0.4631
	low vs medium	1.037	0.654	1.597	0.8738
	low vs high	0.995	0.543	1.707	0.9861
DVT	overall	1.027	0.922	1.138	0.6139
	low vs medium	1.044	0.669	1.589	0.8432
	low vs high	0.932	0.510	1.593	0.8059
MI	overall	1.413	1.170	1.696	0.0002
	low vs medium	3.657	1.434	9.629	0.0066
	low vs high	5.301	1.935	14.525	0.0009
Myocardial injury	overall	1.367	1.271	1.472	< 0.0001
	low vs medium	2.367	1.729	3.241	< 0.0001
	low vs high	4.183	2.951	5.937	< 0.0001
Acute HF	overall	2.036	1.805	2.312	< 0.0001
	low vs medium	8.250	3.795	19.863	< 0.0001
	low vs high	35.559	17.502	82.275	< 0.0001
Stroke/TIA	overall	1.243	1.062	1.441	0.0049
	low vs medium	3.124	1.620	6.047	0.0006
	low vs high	2.039	0.786	4.731	0.1137
Complete RF	overall	1.193	1.048	1.364	0.0083

	low vs medium	1.230	0.710	2.136	0.4611
	low vs high	2.012	1.096	3.754	0.0256
SIRS	overall	1.024	0.942	1.110	0.569
	low vs medium	0.801	0.553	1.139	0.229
	low vs high	1.295	0.865	1.896	0.1949
Sepsis	overall	1.358	1.115	1.643	0.0018
	low vs medium	2.506	0.884	6.821	0.0424
	low vs high	3.737	1.312	10.228	0.0103
AKI	overall	1.317	1.226	1.413	< 0.0001
	low vs medium	1.856	1.340	2.555	0.0002
	low vs high	3.231	2.274	4.558	< 0.0001
ALD	overall	1.258	1.107	1.423	0.0003
	low vs medium	2.031	1.147	3.544	0.0133
	low vs high	2.396	1.216	4.504	0.0084
MODS	overall	1.169	0.977	1.379	0.0743
	low vs medium	1.100	0.455	2.406	0.8207
	low vs high	2.001	0.825	4.397	0.0994
All-cause bleedings	overall	1.172	1.057	1.294	0.002
	low vs medium	1.133	0.693	1.796	0.6068
	low vs high	2.124	1.291	3.396	0.0022
Intracranial bleeding	overall	1.076	0.828	1.351	0.5528
	low vs medium	1.937	0.755	4.710	0.1503
	low vs high	0.429	0.024	2.191	0.4173
Respiratory-tract bleeding	overall	1.066	0.868	1.280	0.5164
	low vs medium	0.497	0.145	1.300	0.1991
	low vs high	1.590	0.625	3.562	0.2883
Upper-GI-tract bleeding	overall	1.315	1.101	1.555	0.0017
	low vs medium	1.658	0.659	3.894	0.2575
	low vs high	3.799	1.622	8.581	0.0015
Lower-GI-tract bleeding	overall	1.129	0.759	1.567	0.5014
	low vs medium	0.479	0.025	2.815	0.4963
	low vs high	1.730	0.253	7.555	0.5032
Urinary tract bleeding	overall	1.273	0.998	1.591	0.0402
	low vs medium	1.283	0.346	3.960	0.6793
	low vs high	2.910	0.888	8.491	0.0572
Pneumonia	overall	1.28	1.21	1.36	<0.001
	low vs medium				
	low vs high	2.28	1.74	3.01	<0.0001

Abbreviations: AKI – acute kidney injury, ALD – acute liver dysfunction, DVT – deep vein thrombosis, HF – heart failure, MI – myocardial infarction, MODS – multiple organ dysfunction syndrome, PE – pulmonary embolism, RF – respiratory failure, TIA – transient ischemic attack, SIRS – systemic inflammatory response syndrome GI – gastrointestinal.

Table S9. Components of C_2HEST score and the risk of outcomes in the univariate Cox proportional hazard model (all-cause death) and competing risk regression model (other outcomes).

Endpoint	Component	OR	CI min.	CI max.	P value
End of hospitalization - death	CAD	2.244	1.573	3.185	< 0.0001
	COPD	1.013	0.549	1.787	0.9659
	Age>75	2.759	2.115	3.596	< 0.0001
	Thyroid disease	0.465	0.283	0.731	0.0015
	Hypertension	1.683	1.280	2.218	0.0002
	HFrEF	1.796	1.267	2.533	0.0009
End of hospitalization - rehabilitation	CAD	0.852	0.517	1.361	0.5164
	COPD	2.193	1.199	3.828	0.0077
	Age>75	0.602	0.419	0.849	0.0048
	Thyroid disease	1.279	0.851	1.874	0.2203
	Hypertension	1.434	1.085	1.896	0.0112
	HFrEF	0.980	0.607	1.543	0.9318
End of hospitalization - full recovery	CAD	0.593	0.429	0.817	0.0014
	COPD	0.533	0.319	0.878	0.0146
	Age>75	0.398	0.320	0.495	< 0.0001
	Thyroid disease	1.485	1.100	2.019	0.0107
	Hypertension	0.675	0.557	0.818	< 0.0001
	HFrEF	0.703	0.514	0.961	0.0275
All-cause shock	CAD	1.001	0.605	1.608	0.9976
	COPD	0.771	0.313	1.628	0.531
	Age>75	0.682	0.461	0.990	0.049
	Thyroid disease	0.791	0.459	1.287	0.37
	Hypertension	2.005	1.440	2.804	< 0.0001
	HFrEF	1.839	1.161	2.867	0.0082
Hypovolemic shock	CAD	NA	0.000	NA	NA
	COPD	2.001	0.314	7.089	0.3588
	Age>75	1.000	0.414	2.221	0.9998
	Thyroid disease	1.839	0.678	4.226	0.1842
	Hypertension	1.151	0.552	2.386	0.7043
	HFrEF	2.504	0.868	6.324	0.0656
Cardiogenic shock	CAD	1.667	0.666	4.039	0.2633
	COPD	2.742	0.852	7.348	0.062
	Age>75	2.451	1.145	5.290	0.0207
	Thyroid disease	0.642	0.149	1.894	0.4791
	Hypertension	0.816	0.369	1.852	0.6178
	HFrEF	4.653	1.896	11.423	0.0007
Septic shock	CAD	1.182	0.674	2.001	0.5458
	COPD	0.566	0.168	1.426	0.2847
	Age>75	0.490	0.302	0.768	0.0026
	Thyroid disease	0.680	0.350	1.208	0.2193
	Hypertension	2.762	1.885	4.089	< 0.0001
PE	HFrEF	1.330	0.766	2.241	0.2962

	CAD	0.515	0.228	1.042	0.0841
	COPD	0.873	0.260	2.198	0.7988
	Age>75	1.020	0.642	1.581	0.9325
	Thyroid disease	0.486	0.203	0.986	0.0695
	Hypertension	1.522	1.023	2.268	0.0383
	HFrEF	1.373	0.734	2.450	0.3
DVT	CAD	0.754	0.106	3.263	0.737
	COPD	1.378	0.074	7.314	0.7621
	Age>75	0.724	0.198	2.110	0.5836
	Thyroid disease	0.885	0.140	3.100	0.8703
	Hypertension	1.058	0.407	2.686	0.905
	HFrEF	1.484	0.293	5.566	0.5906
MI	CAD	1.574	0.548	4.162	0.3757
	COPD	NA	0.000	NA	NA
	Age>75	1.547	0.649	3.594	0.3133
	Thyroid disease	0.571	0.091	1.976	0.4535
	Hypertension	1.642	0.665	4.316	0.293
	HFrEF	3.283	1.225	8.567	0.0158
Myocardial injury	CAD	1.336	0.889	1.990	0.1586
	COPD	1.472	0.801	2.658	0.2045
	Age>75	1.970	1.468	2.640	< 0.0001
	Thyroid disease	0.752	0.466	1.180	0.2275
	Hypertension	1.379	1.024	1.861	0.0348
	HFrEF	2.058	1.403	3.012	0.0002
acute HF	CAD	1.395	0.775	2.476	0.2605
	COPD	0.538	0.151	1.484	0.2771
	Age>75	3.745	2.209	6.470	< 0.0001
	Thyroid disease	0.539	0.212	1.190	0.1553
	Hypertension	1.175	0.642	2.206	0.6064
	HFrEF	13.248	7.359	24.524	< 0.0001
Stroke/TIA	CAD	1.231	0.465	2.869	0.6503
	COPD	0.467	0.026	2.242	0.4583
	Age>75	1.870	0.967	3.547	0.0576
	Thyroid disease	0.753	0.223	1.904	0.5943
	Hypertension	2.424	1.230	5.005	0.0127
	HFrEF	0.844	0.315	2.003	0.7163
Complete RF	CAD	1.753	0.890	3.523	0.1079
	COPD	1.041	0.391	2.864	0.9355
	Age>75	1.317	0.788	2.208	0.2939
	Thyroid disease	0.851	0.392	1.846	0.6801
	Hypertension	0.825	0.483	1.400	0.4776
	HFrEF	1.806	0.924	3.602	0.0869
Pneumonia	CAD	0.858	0.621	1.188	0.3537
	COPD	1.573	0.942	2.717	0.0923
	Age>75	1.219	0.977	1.522	0.0796
	Thyroid disease	1.096	0.823	1.462	0.5332

SIRS	Hypertension	2.348	1.948	2.834	< 0.0001
	HFrEF	1.398	1.013	1.940	0.043
	CAD	0.905	0.538	1.472	0.6974
	COPD	1.274	0.599	2.454	0.4962
	Age>75	1.021	0.716	1.435	0.9086
	Thyroid disease	0.611	0.346	1.007	0.0686
Sepsis	Hypertension	0.857	0.630	1.161	0.321
	HFrEF	1.600	1.003	2.505	0.0437
	CAD	0.415	0.088	1.438	0.2045
	COPD	1.919	0.278	8.028	0.426
	Age>75	1.201	0.451	3.073	0.7051
	Thyroid disease	0.550	0.086	1.960	0.4302
AKI	Hypertension	1.521	0.567	4.352	0.4138
	HFrEF	5.293	1.856	15.129	0.0017
	CAD	1.639	1.095	2.422	0.0146
	COPD	1.182	0.613	2.138	0.598
	Age>75	1.274	0.931	1.732	0.1251
	Thyroid disease	0.515	0.295	0.846	0.0132
ALD	Hypertension	2.423	1.777	3.328	< 0.0001
	HFrEF	1.529	1.027	2.252	0.0336
	CAD	1.052	0.477	2.154	0.895
	COPD	0.295	0.016	1.401	0.2325
	Age>75	1.686	0.972	2.879	0.0583
	Thyroid disease	0.863	0.353	1.807	0.7206
MODS	Hypertension	1.495	0.866	2.619	0.1525
	HFrEF	1.854	0.917	3.597	0.0755
	CAD	0.748	0.251	1.969	0.5761
	COPD	1.034	0.161	3.713	0.9653
	Age>75	0.475	0.183	1.089	0.0978
	Thyroid disease	0.418	0.067	1.401	0.2361
All-cause bleedings	Hypertension	1.403	0.672	2.958	0.3669
	HFrEF	4.681	1.923	10.941	0.0005
	CAD	1.057	0.557	1.911	0.8602
	COPD	0.764	0.225	1.943	0.615
	Age>75	1.027	0.643	1.604	0.9104
	Thyroid disease	1.884	1.117	3.047	0.0129
Intracranial bleeding	Hypertension	1.267	0.837	1.921	0.2629
	HFrEF	1.729	0.962	3.017	0.0597
	CAD	0.357	0.019	1.908	0.3328
	COPD	NA	NA	NA	NA
	Age>75	1.457	0.524	3.731	0.4459
	Thyroid disease	0.386	0.021	1.879	0.3554
Respiratory-tract bleeding	Hypertension	2.602	1.018	7.171	0.0511
	HFrEF	0.733	0.109	2.860	0.695
	CAD	1.584	0.536	4.249	0.38
	COPD	0.520	0.028	2.682	0.5339

	Age>75	0.217	0.051	0.640	0.0146
	Thyroid disease	1.355	0.453	3.294	0.5396
	Hypertension	1.358	0.635	2.902	0.4256
	HFrEF	2.506	0.876	6.622	0.0734
	CAD	0.627	0.166	1.879	0.4408
	COPD	1.473	0.229	5.305	0.6119
Upper-GI-tract bleeding	Age>75	1.898	0.858	4.089	0.1051
	Thyroid disease	2.713	1.119	5.930	0.0174
	Hypertension	1.175	0.544	2.592	0.6826
	HFrEF	2.040	0.740	5.169	0.1468
	CAD	4.604	0.639	21.975	0.0749
	COPD	NA	0.000	NA	NA
	Age>75	2.030	0.402	8.419	0.3448
Lower-GI-tract bleeding	Thyroid disease	7.582	1.843	29.240	0.003
	Hypertension	0.669	0.152	2.748	0.5758
	HFrEF	NA	NA	NA	NA
	CAD	0.903	0.182	3.404	0.8889
	COPD	1.127	0.060	6.041	0.9107
	Age>75	1.227	0.398	3.436	0.7054
UTB	Thyroid disease	1.525	0.348	4.724	0.511
	Hypertension	1.355	0.482	3.981	0.5668
	HFrEF	2.443	0.642	8.208	0.1636

Abbreviations: AKI – acute kidney injury, ALD – acute liver dysfunction, CAD – coronary artery disease, COPD - Chronic obstructive pulmonary disease, DVT – deep vein thrombosis, HF – heart failure, HFrEF – heart failure with reduced ejection fraction, MI – myocardial infarction, MODS – multiple organ dysfunction syndrome, PE – pulmonary embolism, RF – respiratory failure, UTB – urinary tract bleeding, TIA – transient ischemic attack, SIRS – systemic inflammatory response syndrome GI – gastrointestinal

Table S10. Clinical non-fatal events and hospitalization outcomes in the C2HEST risk strata.

Variables, units (N)	**Low risk [0-1]** mean±SD min-max (N) or n/N (% of risk category)	**Medium risk [2-3]** mean±SD min-max (N) or n/N (% of risk category)	**High risk [>4]** mean±SD min-max (N) or n/N (% of risk category)	**OMNIBUS *p-value***	***p-value* (for post-hoc analysis)**
Hospitalization					
Duration of hospitalization, days (2184)	11.6±14.0 1 - 131	13.2±13.6 1 - 124	16.1±15.9 1 - 121	<0.0001	0.064 [a], <0.0001[b], 0.0301[c]
Admission at ICU (2184)	148/1418(10.4%)	39/492 (7.9%)	27/274 (9.9%)		
End of hospitalisation					
death	119/1418 (8.4%)	110/492 (22.4%)	97/274 (35.5%)	<0.0001	<0.0001[a, b], 0.00495 [c]
discharge home – full recovery	993/1418(70.0%)	220/492 (44.7%)	103/274 (37.6%)		
transfer to another hospital – worsening	139/1418 (9.8%)	97/492 (19.7%)	44/274 (16.1%)		
transfer to another hospital – in recovery	167/1418(11.8%)	65/492 (13.2%)	30/274 (10.9%)		
Clinical events					
Aborted cardiac arrest (2184)	15/1418 (1.1%)	3/492 (0.6%)	6/274 (2.2%)	0.155	N/A
Shock (2184)	109/1418 (7.7%)	46/492 (9.3%)	33/274 (12.0%)	0.049	N/A
Hypovolemic shock	22/1418 (1.6%)	7/492 (1.4%)	6/274 (2.2%)	0.665	N/A
Cardiogenic shock	7/1418 (0.5%)	11/492 (2.2%)	14/274 (5.1%)	<0.0001	0.0046 [a], <0.0001[b], 0.161[c]
Septic shock	89/1418 (6.3%)	30/492 (6.1%)	22/274 (8.0%)	0.521	N/A
Venous thromboembolic disease (2184)	47/1418 (3.4%)	13/492 (2.6%)	9/274 (3.3%)	0.911	N/A
Pulmonary embolism (2184)	39/1418 (2.7%)	11/492 (2.2%)	11/274 (3.3%)		N/A
Deep vein thrombosis (2184)	8/1418 (0.6%)	2/492 (0.4%)	0/274 (0.0%)		N/A
MI (2184)	8/1418 (0.6%)	10/492 (2.0%)	8/274 (2.9%)	0.00054	0.0334 [a], 0.00503 [b], 1.0 [c]
Acute HF (2184)	8/1418 (0.6%)	22/492 (4.5%)	46/274 (16.8%)	<0.0001	<0.0001[a, b, c]
Stroke/TIA (2184)	18/1418 (1.3%)	19/492 (3.9%)	7/274 (2.6%)	0.00158	0.00199 [a], 0.54 [b], 1.0 [c]
New cognitive signs and symptoms (2184)	38/1418 (2.7%)	51/492 (10.4%)	32/274 (11.7%)	<0.0001	<0.0001[a], <0.0001[b], 1.0 [c]
Pneumonia (2184)	606/1418(42.7%)	279/492 (56.7%)	176/274 64.2%)	<0.0001	<0.0001[a], <0.0001[b], 0.151[c]
SIRS (2115)	141/1353(10.5%)	42/489 (8.6%)	36/273 (13.2%)	0.135	N/A
Sepsis (884)	9/576 (1.6%)	7/183 (3.8%)	7/125 (5.6%)	0.0155	0.23 [a], 0.0405 [b], 1.0 [c]
AKI (2184)	111/1418 (7.8%)	67/492 (13.6%)	59/274 (21.5%)	<0.0001	0.0006[a], <0.0001[b], 0.019 [c]
ALD (1975)	30/1257 (2.4%)	22/465 (4.7%)	14/253 (5.5%)	0.00643	0.054 [a], 0.0362 [b], 1.0 [c]
MODS (2184)	21/1418 (1.5%)	8/492 (1.6%)	8/274 (2.9%)	0.238	N/A
LA (245)	9/105 (8.6%)	5/79 (6.3%)	8/61 (13.1%)	0.372	N/A
Hyperlactaemia (245)	78/105 (74.3%)	52/79 (65.8%)	37/61 (60.7%)	0.166	N/A
Bleedings (2184)	64/1418 (4.5%)	25/492 (5.1%)	25/274 (9.1%)	0.00711	1.0 [a], 0.0086 [b], 0.131 [c]
intracranial (2184)	12/1418 (0.8%)	8/492 (1.6%)	1/274 (0.4%)	0.226	N/A
respiratory (2184)	23/1418 (1.6%)	4/492 (0.8%)	7/274 (2.6%)	0.158	N/A
gastrointestinal (2184)	20/1418 (1.4%)	9/492 (1.8%)	12/274 (4.3%)	0.0164	1.0 [a], 0.0105 [b], 0.29 [c]
urinary tract (2184)	9/1418 (0.6%)	4/492 (0.8%)	5/274 (1.8%)	0.151	N/A

Continuous variables are presented as mean±SD range (minimum-maximum) and a number of non-missing values.

Categorized variables are presented as a number with a percentage.

Abbreviations: N-valid measurements, n - number of patients with parameter above cut-off point, SD - standard deviation, ANOVA - analysis of variance, ICU - intensive care unit, MI - myocardial infarction, HF - heart failure,

TIA -transient ischemic attack, SIRS - systemic inflammatory response syndrome, AKI – acute kidney injury, ALD – acute liver dysfunction MODS - multiple organ dysfunction syndrome, LA - lactic acidosis, N/A – not-applicable, a – low risk vs. medium risk, b – low risk vs. high risk, c – medium risk vs. high risk.

Table S11. Discriminatory performance of the C_2HEST score on the clinical events

Clinical event	AUC	Sensitivity	Specificity
End of hospitalization - full recovery	0.66	0.75	0.51
End of hospitalization - deterioration	0.59	0.50	0.67
End of hospitalization - rehabilitation	0.51	0.62	0.42
End of hospitalization - death	0.71	0.64	0.70
All-cause shock	0.58	0.74	0.437
Hypovolemic shock	0.55	0.71	0.42
Cardiogenic shock	0.77	0.78	0.66
Septic shock	0.56	0.74	0.42
PE	0.52	0.63	0.42
DVT	0.48	0.10	0.97
Venous thromboembolic disease	0.51	0.63	0.42
MI	0.72	0.69	0.65
Myocardial injury	0.67	0.62	0.64
Acute HF	0.86	0.90	0.67
Stroke/TIA	0.64	0.59	0.65
Complete RF	0.58	0.22	0.92
SIRS	0.49	0.16	0.87
Sepsis	0.69	0.57	0.75
AKI	0.65	0.79	0.44
ALD	0.64	0.85	0.40
MODS	0.58	0.38	0.76
All bleedings	0.57	0.222	0.88
Intracranial bleeding	0.56	0.38	0.76
Respiratory tract bleeding	0.51	0.21	0.88
Upper GI tract bleeding	0.64	0.56	0.65
Lower GI tract bleeding	0.61	0.89	0.41
UTB	0.60	0.28	0.93
Gynecological bleeding	0.63	0.929	0.35
Pneumonia	0.62	0.69	0.53

Abbreviations: AKI – acute kidney injury, ALD – acute liver dysfunction, DVT – deep vein thrombosis, HF – heart failure, MI – myocardial infarction, MODS – multiple organ dysfunction syndrome, PE – pulmonary embolism, RF – respiratory failure, UTB – urinary tract bleeding, TIA – transient ischemic attack, SIRS – systemic inflammatory response syndrome GI – gastrointestinal

Table S12. Hazard ratio for the in-hospital all-cause-death for modified C2HEST risk stratification. The "thyroid disease" has been replaced by "hypothyroidism" and "age>75 years" by "age>65 years", respectively

Total deaths	**HR**	**CI min.**	**CI max.**	**p-*value***
overall	1.437041	1.380787	1.495586	<0.0001
low vs medium	4.119509	3.139181	5.405980	<0.0001
low vs high	6.654120	5.158194	8.583878	<0.0001

HR – hazard ratio

Table S13. Odds ratios for quantifying the strength of the association between the modified CH2EST-score and study endpoints and adverse events - the "thyroid disease" has been replaced by "hypothyroidism" and cut-off point for age to ">65 years" as scoring items.

Endpoint	Comparison	OR	CI min.	CI max.	P value
End of hospitalization - death	overall	1.541	1.443	1.648	< 0.0001
	low vs medium	3.990	2.696	6.026	< 0.0001
	low vs high	8.098	5.655	11.912	< 0.0001
End of hospitalization - deterioration	overall	1.183	1.106	1.264	< 0.0001
	low vs medium	2.688	1.926	3.783	< 0.0001
	low vs high	2.400	1.734	3.352	< 0.0001
End of hospitalization - rehabilitation	overall	1.055	0.983	1.131	0.1367
	low vs medium	1.276	0.921	1.766	0.142
	low vs high	1.296	0.953	1.766	0.0984
End of hospitalization - full recovery	overall	0.693	0.658	0.730	< 0.0001
	low vs medium	0.338	0.268	0.425	< 0.0001
	low vs high	0.225	0.181	0.280	< 0.0001
All-cause shock	overall	1.191	1.100	1.287	< 0.0001
	low vs medium	1.720	1.146	2.590	0.0089
	low vs high	2.284	1.583	3.336	< 0.0001
Hypovolemic shock	overall	1.057	0.877	1.261	0.5459
	low vs medium	1.134	0.454	2.757	0.7813
	low vs high	1.549	0.711	3.482	0.274
Cardiogenic shock	overall	1.582	1.326	1.894	< 0.0001
	low vs medium	2.438	0.733	9.342	0.1566
	low vs high	6.066	2.296	20.865	0.001
Septic shock	overall	1.166	1.065	1.274	0.0008
	low vs medium	1.709	1.079	2.724	0.0227
	low vs high	2.163	1.424	3.338	0.0004
PE	overall	1.111	1.007	1.224	0.0034
	low vs medium	1.243	0.759	2.024	0.3831
	low vs high	1.712	1.112	2.664	0.0015
DVT	overall	1.003	0.780	1.262	0.9785
	low vs medium	2.328	0.860	6.874	0.1036
	low vs high	0.940	0.270	3.132	0.9184
MI	overall	1.493	1.230	1.818	< 0.0001
	low vs medium	4.182	0.960	28.610	0.0803
	low vs high	10.380	2.983	65.446	0.0017
Myocardial injury	overall	1.386	1.288	1.495	< 0.0001
	low vs medium	2.893	1.898	4.498	< 0.0001
	low vs high	4.753	3.225	7.188	< 0.0001
acute HF	overall	1.988	1.748	2.277	< 0.0001
	low vs medium	9.890	2.750	63.140	0.0025
	low vs high	36.730	11.434	224.515	< 0.0001
Stroke/TIA	overall	1.232	1.055	1.433	0.0073
	low vs medium	2.276	0.953	5.781	0.0692
	low vs high	3.315	1.535	7.949	0.0038
Complete RF	overall	1.191	1.046	1.361	0.0092
	low vs medium	0.770	0.376	1.574	0.4731
	low vs high	1.554	0.810	2.989	0.184
Pneumonia	overall	1.287	1.225	1.355	< 0.0001
	low vs medium	2.606	2.103	3.234	< 0.0001

	low vs high	3.044	2.480	3.742	< 0.0001
	overall	1.041	0.964	1.123	0.3033
SIRS	low vs medium	0.963	0.675	1.368	0.8349
	low vs high	1.027	0.739	1.426	0.874
	overall	1.407	1.149	1.727	0.0009
Sepsis	low vs medium	0.878	0.179	3.614	0.8599
	low vs high	3.660	1.399	11.364	0.013
	overall	1.349	1.257	1.449	< 0.0001
AKI	low vs medium	2.921	1.949	4.447	< 0.0001
	low vs high	4.507	3.113	6.678	< 0.0001
	overall	1.184	1.040	1.344	0.0098
ALD	low vs medium	2.859	1.421	6.121	0.0044
	low vs high	2.935	1.508	6.154	0.0024
	overall	1.205	1.016	1.421	0.0285
MODS	low vs medium	1.249	0.493	3.117	0.631
	low vs high	2.056	0.961	4.657	0.0699
	overall	1.123	1.015	1.240	0.0225
All bleedings	low vs medium	0.882	0.522	1.464	0.6315
	low vs high	1.478	0.963	2.286	0.0753
	overall	1.063	0.834	1.330	0.6066
Intracranial bleeding	low vs medium	0.591	0.127	2.135	0.4472
	low vs high	1.784	0.699	4.871	0.2337
	overall	1.075	0.891	1.283	0.4378
Respiratory tract bleeding	low vs medium	0.549	0.195	1.359	0.2172
	low vs high	0.977	0.455	2.071	0.952
	overall	1.202	1.001	1.434	0.0443
Upper GI tract bleeding	low vs medium	2.803	1.082	8.089	0.0404
	low vs high	2.663	1.063	7.554	0.0458
	overall	1.057	0.722	1.483	0.7568
Lower GI tract bleeding	low vs medium	6.967	1.120	133.657	0.0767
	low vs high	3.394	0.433	68.690	0.2904
	overall	1.268	0.997	1.600	0.0469
UTB	low vs medium	0.229	0.012	1.347	0.1733
	low vs high	2.084	0.789	6.076	0.1499

Abbreviations: AKI – acute kidney injury, ALD – acute liver dysfunction, DVT – deep vein thrombosis, HF – heart failure, MI – myocardial infarction, MODS – multiple organ dysfunction syndrome, PE – pulmonary embolism, RF – respiratory failure, UTB – urinary tract bleeding, TIA – transient ischemic attack, SIRS – systemic inflammatory response syndrome GI – gastrointestinal

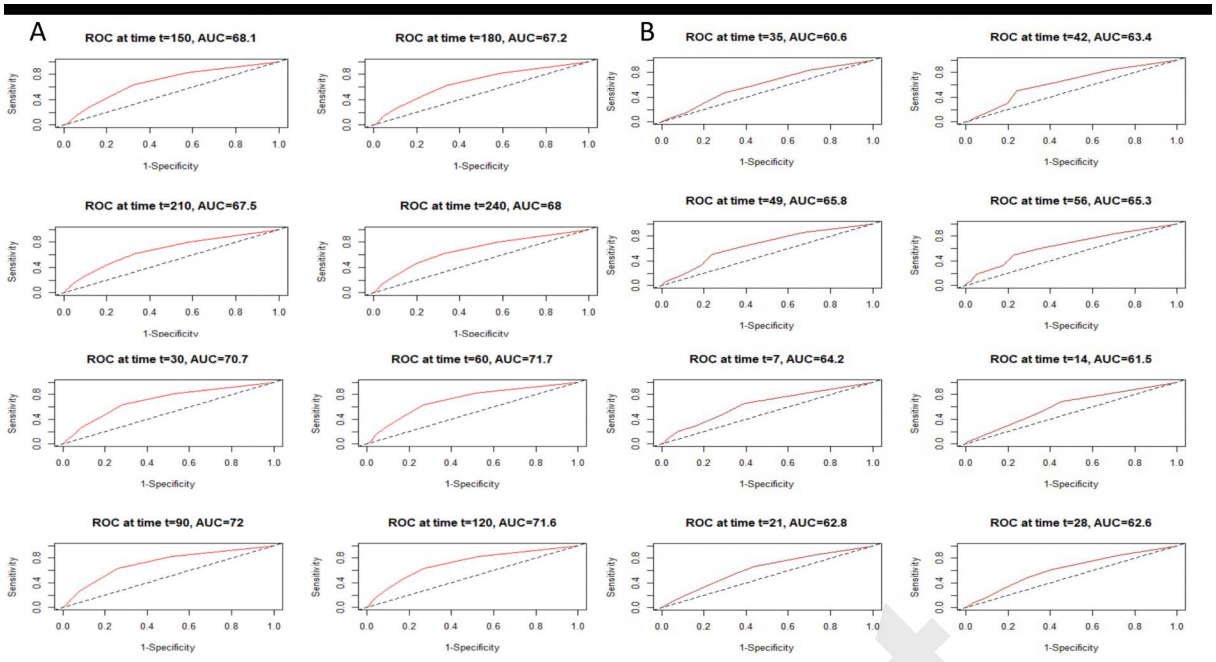


Figure 1. Time-dependent receiver operating characteristic (time-ROC) curves for the C2HEST score in predicting total (A) and in-hospital mortality.

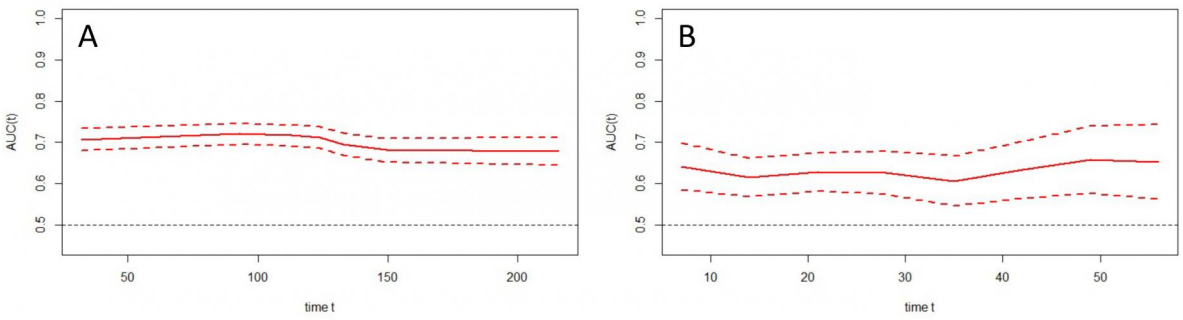


Figure 2. Time-dependent ROC analysis for the C2HEST predictive abilities of all-cause death (A) and death during hospitalization (B) (AUC with CI).

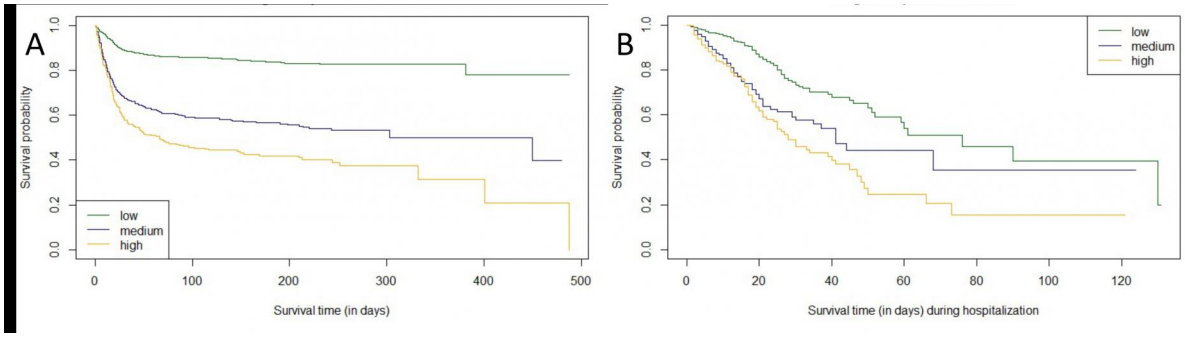
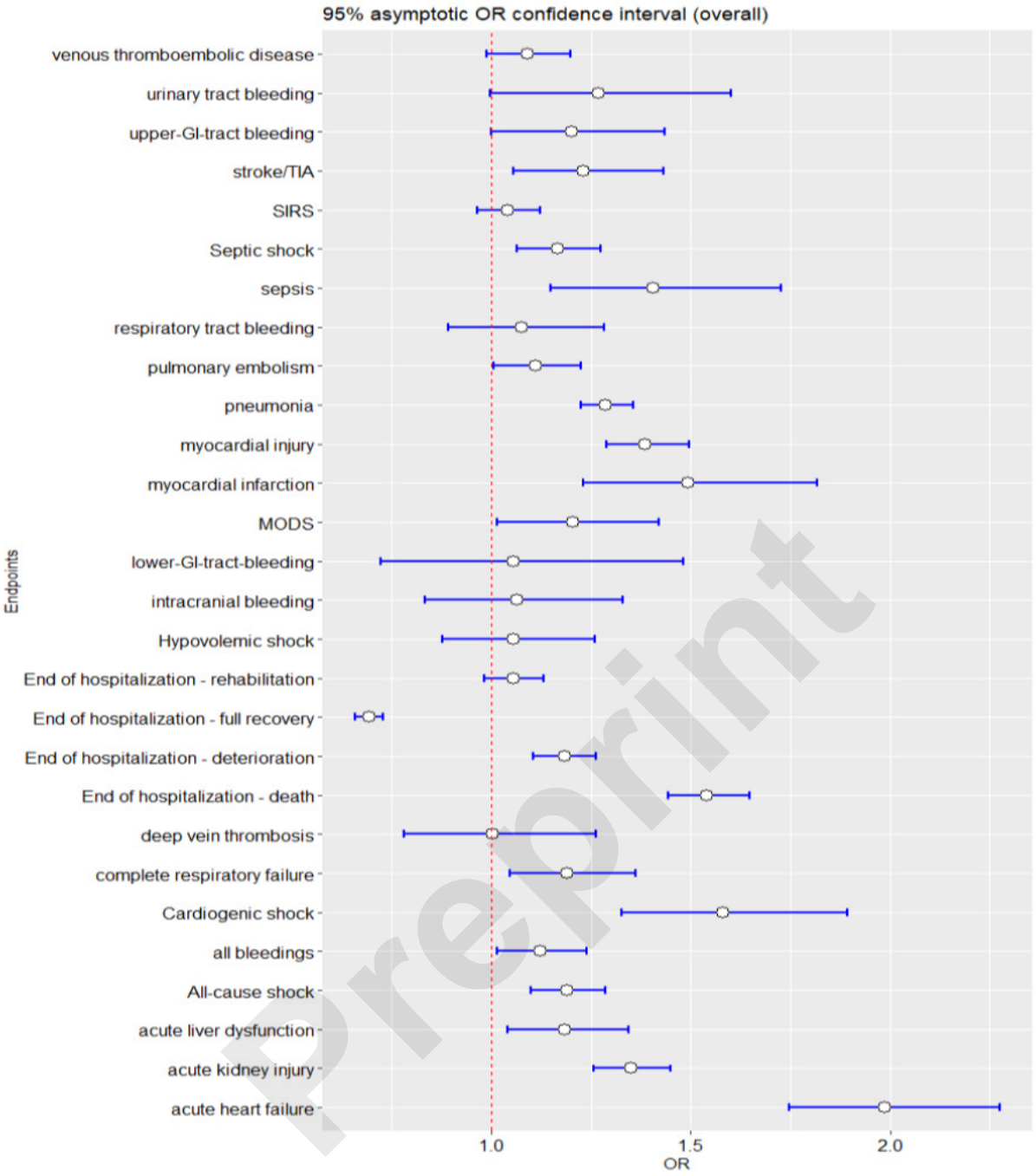
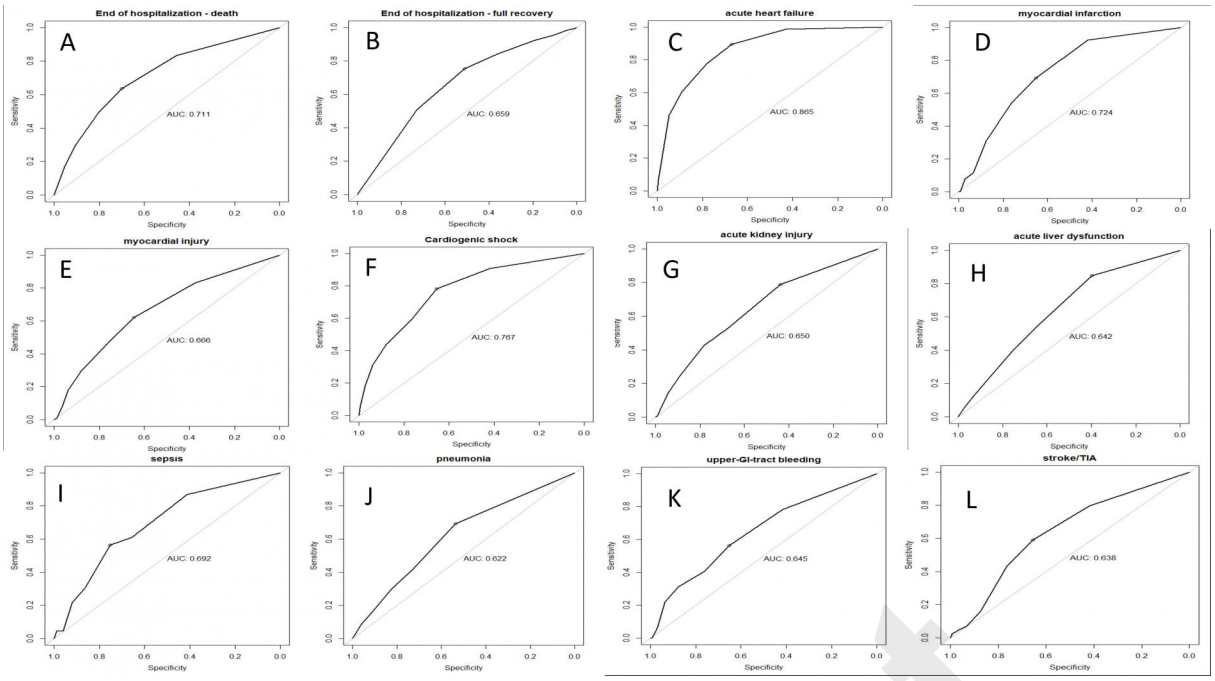


Figure 3. Analysis of the survival curves (A) and in-hospital survival (B) for the low, medium, and high C2HEST risk strata (Kaplan-Meier curve, log-rank p-value <0.0001)



Additional file 10. The overall odds ratio for quantifying the strength of the association of C2HEST -score with study endpoints.



Additional file 15. Receiver operating characteristic (ROC) curves for the modified C2HEST score - replacing “thyroid disease” with “hypothyroidism” and cut-off point for age to “>65 years” as scoring items in predicting in-hospital death (A), full recovery (B), acute heart failure (C), myocardial infarction (D), myocardial injury (E), cardiogenic shock (F), acute kidney injury (G), acute liver dysfunction (H), sepsis (I), pneumonia (J), upper-GI-bleeding (K), stroke/TIA (L).