**Article**

**Sex-Dependent Differences in Predictive Value of the C2HEST Score in Subjects with COVID-19—A Secondary Analysis of the COLOS Study**

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Abstract: Background: Since the outbreak of the COVID-19 pandemic, a growing number of evidence suggests that COVID-19 presents sex-dependent differences in clinical course and outcomes. Nevertheless, there is still an unmet need to stratify the risk for poor outcome at the beginning of hospitalization. Since individual C₂HEST components are similar COVID-19 mortality risk factors, we evaluated sex-related predictive value of the score. Material and Methods: A total of 2183 medical records of consecutive patients hospitalized due to confirmed SARS-CoV-2 infections were analyzed. Subjects were assigned to one of two of the study arms (male vs. female) and afterward allocated to different stratum based on the C₂HEST score result. The measured outcomes included: in-hospital-mortality, three-month- and six-month-all-cause-mortality and in-hospital non-fatal adverse clinical events. Results: The C₂HEST score predicted the mortality with better sensitivity in female population regarding the short- and mid-term. Among secondary outcomes, C₂HEST-score revealed predictive value in both genders for pneumonia, myocardial injury, myocardial infarction, acute heart failure, cardiogenic shock, and acute kidney injury. Additionally in the male cohort, the C₂HEST value predicted acute liver dysfunction and all-cause bleeding, whereas in the female arm-stroke/TIA and SIRS. Conclusion: In the present study, we demonstrated the better C₂HEST-score predictive value for mortality in women and illustrated sex-dependent differences predicting non-fatal secondary outcomes.

Keywords: risk factors; COVID-19; SARS-CoV-2; predicting value; mortality; C₂HEST score; gender differences

1. Introduction

Since the outbreak in 2019 in China of the coronavirus disease (COVID-19), the pandemic has revealed an unprecedented impact on the global health care system, with over 450 million confirmed cases resulting in approximately 6 million of deaths reported worldwide [1]. From the initial phase of the pandemic, a growing number of evidence [2] suggests that COVID-19 presents significant sex-dependent differences in clinical course and mortality.

The clinical manifestation of COVID-19 remains unpredictable and varies from asymptomatic to severe or lethal [3–5]. Hence, there is an urgent need to introduce a simple and fast triage tool to clinical practice aimed at supporting the decision-making process for the clinicians in terms of appropriate management and optimized use of limited resources.

The C₂HEST score was originally designed [6] to predict the potential development of atrial fibrillation (AF) in the general population. Lately, a growing body of evidence has appeared, illustrating that the C₂HEST score can predict poor outcomes of patients in severe clinical conditions. Our previous study demonstrated the usefulness of the C₂HEST-score in predicting the adverse COVID-19-outcomes in hospitalized subjects with type 2 diabetes mellitus. Since male sex is postulated to be an independent risk factor of an unfavorable COVID-19 outcome, we aimed to assess the sex-dependent predictive value of the C₂HEST-score.

2. Materials and Methods

2.1. Study Design and Population

The study population consisted of 2183 consecutive patients with confirmed by reverse transcription-polymerase chain reaction (RT-PCR) infection of SARS-CoV-2 admitted to the Medical University COVID-19 Center. All subjects were hospitalized between February 2020 and June 2021. The study protocol has been approved by the Institutional Review Board and Ethics Committee at the Wroclaw Medical University, Wroclaw, Poland (No: KB-444/2021). All medical data were fully anonymized and retrospectively analyzed. Due to the character of the study protocol written informed consent from participants was not required. Subjects were assigned to one of two of the study arms male vs. female. Subsequently, all patients were assigned into one C₂HEST score stratum. The C₂HEST score value was calculated depending on originally proposed variables; coronary artery disease
(CAD) (1 point), chronic obstructive pulmonary disease (COPD) (1 point), hypertension (1 point), elderly (age ≥ 75 years, 2 points), systolic heart failure (HF) (2 points), and thyroid disease (1 point). Based on the calculated score subjects were allocated to one of three stratum - low-risk 0 or 1 point, medium-risk 2 or 3 points, and high-risk 4 and more points.

2.2. Follow-Up and Outcomes

The primary clinical outcome was an in-hospital, three-month-, and six-month-all-cause mortality. Other clinical outcomes focused on in-hospital: end of hospitalization other than death (discharge, deterioration or recovery with subsequent transfer to another hospital) advanced mechanical ventilation support, shock, multiple organ dysfunction syndrome (MODS), systemic inflammatory response syndrome (SIRS), sepsis. Also, other clinical features were collected symptomatic bleeding, pneumonia, pulmonary embolism, acute heart failure, myocardial injury, stroke, acute kidney injury, acute liver dysfunction.

2.3. Statistical Analysis

Statisticians with experience in medical academic research performed the analyses to this manuscript. The R language version 4.0.4 with additional packages-pROC and time-ROC [7], survival [8], coin [9], and odds ratio was used for the purpose of data analysis [10] A level of 0.05 was set as significance value.

Descriptive data regarding categorical variables are shown as numbers and percentages, whereas for numerical variables as mean with standard deviation, range (minimum-maximum) along with the number of non-missing values. The omnibus and chi-square tests were performed for categorical variables which exceeded five expected cases in each group. The Fisher exact test was performed for subjects with fewer cell counts. The Welch’s ANOVA was set up for continuous variables in order to adjust for unequal variances between the risk-strata and sample size large sufficient for appropriateness of asymptotic results. For continuous variables, the Games-Howell’s variant of Tukey correction was performed as a part of a post-hoc analysis. On the other hand, for categorical variables, the post-hoc test was analogous to the omnibus test. However, it was performed in subgroups with a Bonferroni correction. Due to a fact that the in-hospital mortality along with the all-cause mortality were available as right-censored data, the time-dependent ROC analysis with inverse probability of censoring weighting (IPCW) was used to estimate them. The time-dependent area under the curve (AUC) was used to assess the C2HEST score and additionally a confirmation of differences in survival curves among risk strata was obtained by a Log-rank test. Proportional hazard assumption was verified using the Grambsch-Therneau test. During analysis of the hazard ratio (HR) in the C2HEST score, its components, as well as risk strata, a Cox proportional hazard model was used. Dichotomic nature of secondary outcomes resulted in the use of a logistic regression model during their analysis. In order to assess predictive capability, the classical receiver operating characteristic (ROC) analysis with an AUC measure was performed. Odds ratio (OR) was presented as a size effect for the influence of the C2HEST score, its components and risk strata.

3. Results

3.1. Baseline Demographical and Clinical Features of the Studied Population

The study population was composed of 2183 subjects at mean age 60.1 ± 18.8 [17–100] A total of 1101 women at mean age 59.3 ± 21.1 [17–100] were enrolled to this study, who were subsequently assigned to the low-risk n = 682 subjects, medium-risk n = 284 patients, and high-risk n = 135 C2HEST strata, respectively. Simultaneously, a total of 1082 males at mean age of 60.8 ± 16.1 [17–99], were assigned to the low-risk (n = 735), medium-risk (n = 208) and high-risk(n = 139). The baseline clinical data of both study cohorts is presented in Table 1. In both cohorts, higher C2HEST risk was related to a higher number of comorbidities and more advanced age.
| Variables | Units | Low Risk | Medium | High Risk | OMNIBUS p-Value | p Value for Post-Hoc Analysis |
|-----------|-------|---------|--------|-----------|----------------|-----------------------------|
|           |       | [0–1]   | [2–3]  | [4]       | Females Males | Females Males |
| Age, years | SD/min-max | N = 682 | N = 735 | N = 284 | N = 208 | Females Males | Females Males |
|           |       | 17–74   | 17–74  | 29–100   | 37–99 | 40–30 | 47–100 | 36–92 | <0.0001 | <0.0001 | 0.0 &<sup>ab</sup> | 0.0004 &<sup>c</sup> | <0.0001 &<sup>b</sup> | 0.115 &<sup>c</sup> |
| Age ≥ 65 years | N/±% | 174 | 175 | 39 | 32 | 27 | 17 | 0.0001 | <0.0001 | <0.0001 &<sup>abc</sup> | <0.0001 &<sup>ab</sup> | <0.0001 &<sup>abc</sup> |
| BMI, kg/m² | mean ± SD/min-max/N | 199 | 198 | 48 | 42 | 17 | 50 | 0.1255 | 0.9609 | N/A | N/A |
| Hypertension | n/±% | 179 | 236 | 213 | 144 | 126 | 123 | 0.0138 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Dyslipidaemia | n/[n/±%]/N | 74 | 138 | 37 | 32 | 27 | 17 | 0.0932 | 0.00011 | N/A | N/A | 0.0191 |
| Atrial fibrillation/flutter | n/[n/±%] | 14 | 35 | 60 | 46 | 65 | 70 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Previous coronary revascularisation | n/[n/±%] | 0 | 6 | 9 | 28 | 35 | 76 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Previous myocardial infarction | n/[n/±%] | 1 | 10 | 18 | 45 | 37 | 80 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Heart failure | n/[n/±%] | 0 | 0 | 20 | 33 | 91 | 111 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Moderate/severe valvular heart disease or previous valve heart surgery | n/[n/±%] | 7 | 6 | 14 | 18 | 26 | 25 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Peripheral artery disease | n/[n/±%] | 1 | 19 | 14 | 17 | 11 | 32 | 0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Previous stroke/TIA | n/[n/±%] | 17 | 30 | 33 | 26 | 24 | 34 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Chronic kidney disease | n/[n/±%] | 33 | 37 | 26 | 44 | 39 | 52 | <0.0001 | <0.0001 | 0.00456 | 0.0083 | <0.0001 | <0.0001 |
| Haemodialysis | n/[n/±%] | 11 | 8 | 5 | 15 | 8 | 11 | 0.01467 | <0.0001 | 1.0 &<sup>b</sup> | 0.9963 | N/A | N/A |
| Asthma | n/[n/±%] | 32 | 22 | 17 | 15 | 16 | 4 | 0.7053 | 0.4996 | N/A | N/A |
| COPD | n/[n/±%] | 1 | 5 | 9 | 16 | 16 | 28 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Hypothyroidism | n/[n/±%] | 1 | 65 | 11 | 56 | 12 | 52 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Hyperthyroidism | n/[n/±%] | 3 | 0.4 | 7 | 2.5 | 3 | 3 | 0.0083 | 0.0009 | 0.1065 | 0.1065 | 0.0081 | 1.0 &<sup>c</sup> |

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; BMI, body mass index; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; OMNIBUS, analysis of variance; N/A, non-applicable; &<sup>a</sup> low risk vs. medium risk, &<sup>b</sup> low risk vs. high risk, &<sup>c</sup> medium risk vs. high risk. Red color text = statistically significant values.

Data regarding the relationship between the C₂HEST score result and treatment applied before hospitalization is shown in the Table 2. In the both cohorts along with increased C₂HEST score, we observed an increasing prevalence drug commonly used in cardiovascular disorders such as angiotensin-converting enzyme inhibitors (ACEI), mineralocorticoid receptor antagonists (MRA), b-blockers, calcium channel blockers, diuretics, statins, vita-
min K antagonists (VKA), novel oral anticoagulants (NOAC), acetylsalicylic acid, P2Y12 inhibitor, metformin, and insulin.

Table 2. Baseline characteristics of the study cohort-treatment applied before hospitalization.

| Variables Units                      | Low Risk [0–1] | Medium [2–3] | High Risk [≥4] | OMNIBUS p-Value for Post-Hoc Analysis |
|--------------------------------------|----------------|--------------|----------------|--------------------------------------|
|                                      | Females N = 682 | Males N = 735 | Females N = 284 | Males N = 208 | Females N = 135 | Males N = 139 | Females N = 135 | Males N = 139 |
| ACEI n/\(n\%)                        | 47 (6.9)       | 69 (9.4)     | 57 (20.1)      | 54 (30.3)   | 62 (40.0)       | <0.0001      | <0.0001       | <0.0001       |
| ARB n/\(n\%)                         | 33 (4.8)       | 43 (5.9)     | 26 (9.2)       | 14 (5.8)    | 16 (10.4)       | 0.0087       | 0.0413       | 0.04855 b |
| MRA n/\(n\%)                         | 3 (0.4)        | 15 (2.0)     | 13 (4.6)       | 20 (9.6)    | 29 (14.8)       | <0.0001      | <0.0001      | <0.0001       |
| β-blocker n/\(n\%)                   | 78 (11.4)      | 119 (16.2)   | 102 (35.9)     | 77 (37.0)   | 81 (56.3)       | <0.0001      | <0.0001      | <0.0001       |
| Calcium channel blocker dihydropiridines n/\(n\%) | 37 (5.4)       | 66 (9.0)     | 48 (16.9)      | 34 (17.2)   | 40 (25.2)       | <0.0001      | <0.0001      | <0.0001       |
| Statin n/\(n\%)                      | 10 (1.5)       | 35 (4.8)     | 28 (13.5)      | 8 (5.9)     | 31 (22.3)       | 0.0113       | <0.0001      | <0.0001       |
| Amiodarone n/\(n\%)                  | 0 (0.1)        | 0 (0.0)      | 0 (0.4)        | 0 (0.5)     | 1 (0.7)         | 0.6165       | 0.1027       | N/A           |
| Thiazide or thiazide-like diuretic n/\(n\%) | 29 (4.3)       | 39 (5.3)     | 36 (12.7)      | 16 (11.9)   | 19 (11.9)       | 0.0001       | 0.0008       | <0.0001       |
| Loop diuretic n/\(n\%)               | 17 (1.9)       | 28 (3.5)     | 29 (8.8)       | 23 (19.2)   | 45 (34.5)       | <0.0001      | <0.0001      | <0.0001       |
| Acetylsalicylic acid n/\(n\%)        | 35 (5.1)       | 46 (6.3)     | 44 (15.5)      | 33 (24.4)   | 49 (35.3)       | <0.0001      | <0.0001      | <0.0001       |
| The second antiplatelet drug n/\(n\%) | 1 (0.1)        | 6 (0.8)      | 5 (1.8)        | 4 (3.0)     | 18 (12.9)       | 0.0009       | <0.0001      | 0.0292 a |
| LMWH n/\(n\%)                        | 32 (4.7)       | 42 (5.7)     | 23 (8.1)       | 11 (8.1)    | 15 (10.8)       | 0.0674       | 0.0535       | N/A           |
| VKA n/\(n\%)                         | 4 (0.6)        | 6 (0.8)      | 6 (2.1)        | 8 (3.8)     | 10 (7.4)        | <0.0001      | <0.0001      | 0.12172 a |
| NOAC n/\(n\%)                        | 6 (0.9)        | 12 (1.6)     | 22 (7.7)       | 15 (7.2)    | 23 (17.0)       | <0.0001      | <0.0001      | <0.0001       |
| Insulin n/\(n\%)                     | 23 (3.4)       | 39 (5.3)     | 14 (4.9)       | 15 (7.2)    | 22 (16.3)       | <0.0001      | 0.0038       | 1.0 a |
| Metformin n/\(n\%)                   | 40 (5.9)       | 64 (8.7)     | 35 (12.3)      | 32 (15.4)   | 22 (16.3)       | <0.0001      | <0.0001      | 0.0011 a |
| Sodium-glucose cotransporter-2 inhibitor n/\(n\%) | 4 (0.6)        | 7 (1.0)      | 4 (1.4)        | 3 (1.4)     | 3 (2.2)         | 0.12658      | 0.018        | N/A           |
| Oral antidiabetics other than SGLT2 inhibitor and metformin n/\(n\%) | 10 (1.5)       | 17 (2.3)     | 20 (7.0)       | 14 (6.7)    | 11 (8.1)        | <0.0001      | <0.0001      | 0.0011 a |
| Proton pump inhibitor n/\(n\%)       | 31 (4.5)       | 58 (7.9)     | 39 (13.7)      | 36 (17.3)   | 49 (27.4)       | <0.0001      | <0.0001      | <0.0001 |

For Post-Hoc Analysis:
- "a" indicates a significant difference from the control group.
- "b" indicates a significant difference from the primary treatment group.
- "c" indicates a significant difference from the secondary treatment group.

Note: Significance levels are indicated for the comparison of treatment groups within each baseline characteristic.
Table 2. Cont.

| Variables                                | Units | Low Risk [0-1] | Medium [2-3] | High Risk [≥4] | OMNIBUS p Value | p Value for Post-Hoc Analysis |
|------------------------------------------|-------|----------------|--------------|----------------|----------------|-----------------------------|
| **Oral corticosteroid**                  | n/n(%)| N = 682        | Males N = 735| Females N = 284| Males N = 208  | Females N = 135             | Males N = 139               |
| **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 the cut-off point; ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; LMWH, low molecular weight heparin; VKA, vitamin K antagonists; NOAC, novel oral anticoagulants; SGLT2 inhibitors, sodium glucose co-transporter-2 inhibitors; OMNIBUS, analysis of variance; N/A, non-applicable; a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red color text = statistically significant values.** |
| **Immuno-suppression other than oral corticosteroid** | n/n(%)| N = 682        | Males N = 735| Females N = 284| Males N = 208  | Females N = 135             | Males N = 139               |
| Females                                  |       | 31 (4.5)       | 31 (4.2)     | 17 (6.0)       | 7 (3.4)        | 5 (3.7)                    | 1 (0.7)                    |
| Males                                    |       | 24 (3.5)       | 25 (3.4)     | 12 (4.2)       | 10 (4.8)       | 2 (1.5)                    | 0 (0.0)                    |
| **Table 3 shows the sex-specific baseline characteristics of patient-reported symptoms, and vital signs during the hospital admission in the studied cohort. The female but not male cohort, had significant differences between the C2HEST strata regarding the prevalence of cough, smell dysfunction, body temperature, and systolic blood pressure, which were decreasing as the score raised. Opposite findings were observed regarding dyspnoea, heart rate, and the diastolic blood pressure.** |

### Table 3. Patient-reported symptoms, vital signs and abnormalities measured during physical examination at hospital admission in the studied cohort.

| Variables                                | Units | Low Risk [0-1] | Medium [2-3] | High Risk [≥4] | OMNIBUS p Value | p Value for Post-Hoc Analysis |
|------------------------------------------|-------|----------------|--------------|----------------|----------------|-----------------------------|
| **Body temperature.**                    | °C    | 37.1 ± 0.8     | 37.1 ± 0.9   | 36.9 ± 0.9     | 36.9 ± 1.0     | 36.8 ± 0.9                 | 37.1 ± 0.8                 |
| **Mean ± SD/min-max/N**                  |       | 35.0–40.5      | 34.4–40.0    | 35.8–40.0      | 35.0–40.0      | 35.2–40.0                  | 35.5–40.0                 |
| **Heart rate, beats/minute mean ± SD/min-max/N** |       | 85.9 ± 14.6    | 86.9 ± 15.6  | 84.6 ± 16.5    | 83.5 ± 17.2    | 82.3 ± 15.8                | 82.3 ± 15.8               |
| **Respiratory rate breaths/minute mean ± SD/min-max/N** |       | 17.9 ± 12.0    | 18.9 ± 16.5  | 17.8 ± 18.0    | 19.6 ± 19.6    | 19.0 ± 19.4                | 19.6 ± 17.6               |
| **Systolic blood pressure mmHg mean ± SD/min-max/N** |       | 128.6 ± 21.3   | 132.6 ± 21.1 | 133.2 ± 24.2   | 136.6 ± 26.7   | 135.6 ± 25.5              | 133.5 ± 24.0             |

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 the cut-off point; ACEI, angiotensin-converting-enzyme inhibitors; ARBs, angiotensin receptor blockers; MRAs, mineralocorticoid receptor antagonists; LMWH, low molecular weight heparin; VKA, vitamin K antagonists; NOAC, novel oral anticoagulants; SGLT2 inhibitors, sodium glucose co-transporter-2 inhibitors; OMNIBUS, analysis of variance; N/A, non-applicable; a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red color text = statistically significant values.
Table 3. Cont.

| Variables Units | Males | Females | Males | Females | Males | Females | Males | Females | p Value | p Value for Post-Hoc Analysis |
|-----------------|-------|---------|-------|---------|-------|---------|-------|---------|---------|-------------------------------|
| Diastolic blood pressure, mmHg mean ± SD/min-max/N | 77.4 ± 12.5 | 77.1 ± 12.7 | 79.3 ± 13.5 | 497 | 550 | 214 | 166 | 0.6167 | 0.0091 N/A | 0.986 b 0.002 b 0.034 c |
| SpO2 on room air, % (FiO2 = 21%) mean ± SD/min-max/N | 94.4 ± 5.6 | 91.1 ± 7.9 | 90.8 ± 8.5 | 242 | 393 | 160 | 121 | <0.001 <0.001 a | 0.0014 a 0.205 b 0.79 c |

Abnormalities detected during physical examination

| Parameter time of assessment | Units | Males | Females | Males | Females | Males | Females | p Value | p Value for Post-Hoc Analysis |
|------------------------------|-------|-------|---------|-------|---------|-------|---------|---------|-------------------------------|
| Leucocytes n/µL | >12 × 10^9/µL | 85 (13.8) | 116 (16.9) | 52 (18.8) | 32 (15.8) | 23 (17.7) | 29 (212) | 0.3085 | 0.3279 N/A N/A |
| Haemoglobin n/µL | <12 g/dL | 172 (28.0) | 173 (25.2) | 91 (32.9) | 104 (51.2) | 63 (48.5) | 84 (61.3) | <0.0001 | <0.0001 a <0.0001 a 0.4836 c <0.001 ab <0.001 ab 0.2546 c 0.0106 a |

Categorized variables are presented as: a number with a percentage. Continuous variables are presented as: mean ± SD, range (minimum - maximum) and number of non-missing values. Information about the numbers with valid values is provided in the left column. Abbreviations: N, valid measurements; n, number of patients with parameter above the cut-off point; SD, standard deviation. OMNIBUS, analysis of variance; N/A, non-applicable.

The detailed characteristics of the laboratory parameters measured during the hospitalization in the study cohort are presented in Tables 4 and 5.

Table 4. Patient initial and on discharge laboratory assay in the studied cohort after C2HEST risk stratification.
### Table 4. Cont.

| Parameter | Time of Assessment | Units | Low Risk [1–0] | Medium [2–3] | High Risk [1–4] | p-Value OMNIBUS | p-Value for Post-Hoc Analysis |
|-----------|--------------------|-------|----------------|-------------|----------------|-----------------|-----------------------------|
| PH        |                    |       | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males |
| On admission |                   |       | 7.42 ± | 7.43 ± | 7.43 ± | 7.43 ± | 7.39 ± | 7.42 ± | 0.2287 | 0.8496 | N/A | N/A |
| SD/min-max/N |                | 0.08 ± | 0.09 | 0.07 | 0.07 | 0.08 | 0.07 | 0.72 | 0.75 | | | |
| PaCO2      | SD/min-max/N      | mmHg  | 7.43 ± | 7.42 ± | 7.43 ± | 7.42 ± | 7.44 ± | 7.40 ± | 0.8782 | 0.5746 | N/A | N/A |
| On discharge |                    |       | 7.22–7.54 | 7.06–7.54 | 7.27–7.53 | 7.01–7.55 | 7.26–7.56 | 7.25–7.52 | | | |
| Lactates   |                    | ± mmol/L | 75.3 ± | 70.2 ± | 80.7 ± | 73.2 ± | 70.7 ± | 70.5 ± | 0.562 | 0.903 | N/A | N/A |
| On admission |                   |       | 12.8–207.0 | 23.5–165.0 | 23.3–286.0 | 28.6–298.0 | 32.8–134.0 | 23.7–222.0 | | | |
| ECO3       | standard mean     | mmol/L | 25.0 ± | 24.9 ± | 24.9 ± | 24.0 ± | 23.4 ± | 24.8 ± | 0.2666 | 0.4967 | N/A | N/A |
| On admission |                   |       | 12.5–32.9 | 12.1–32.8 | 16.9–39.5 | 14.3–32.4 | 13.5–32.3 | 17.3–36.6 | | | |
| BE         | mean ± SD/min-max/N | mmol/L | 0.63 ± | 1.12 ± | 2.96 ± | 0.88 ± | [–0.1 ± | 2.92 ± | 0.2745 | 0.4315 | N/A | N/A |
| On admission |                   |       | 5.06 | 4.67 | 4.72 | 5.59 | 4.75 | 7 | 17 | | |
| Lactates   | mean ± SD/min-max/N | mmol/L | 2.0 ± | 2.7 ± | 2.0 ± | 2.0 ± | 2.9 ± | 2.1 ± | 0.1027 | 0.0291 | N/A | 0.396 | 0.913 |
| On admission |                   |       | 0.6–4.3 | 1.1–12.8 | 0.6–5.7 | 0.5–3.8 | 0.8–12.0 | 0.6–5.7 | 0.0004 | 0.0011 | N/A | N/A |
| Na         | mean ± SD/min-max/N | mmol/L | 138.3 ± | 138.2 ± | 137.7 ± | 137.7 ± | 137.6 ± | 137.6 ± | 0.4803 | 0.3745 | N/A | N/A |
| On admission |                   |       | 106.3–155.0 | 109.0–159.0 | 101.0–175.0 | 105.0–158.0 | 108.0–174.0 | 112.0–158.0 | 137 | | |
| K          | mean ± SD/min-max/N | mmol/L | 3.99 ± | 4.13 ± | 4.06 ± | 4.25 ± | 4.14 ± | 4.43 ± | 0.0403 | 0.0002 | N/A | N/A |
| On admission |                   |       | 2.33–6.5 | 2.0–7.5 | 2.42 ± | 2.4–7.0 | 2.53–6.6 | 2.87 | 0.0004 | 0.0011 | N/A | N/A |

### Electrolytes, inflammatory and iron biomarkers

- PH: Acid-base balance in the arterial blood gas
- PaCO2: Partial pressure of carbon dioxide
- BE: Base excess
- ECO3: Standard bicarbonate
- Lactates: Lactate concentration
- Na: Sodium concentration
- K: Potassium concentration

The table provides values and comparisons for various parameters across different risk levels, including mean and standard deviation (SD) values for each parameter.
Table 4. Cont.

| Parameter                                                                 | Time of Assessment | Units          | Low Risk [0–1] | Medium [2–3] | High Risk [4–] | p-Value | p-Value for Post-Hoc Analysis |
|--------------------------------------------------------------------------|--------------------|----------------|----------------|--------------|---------------|---------|-------------------------------|
|                                                                          |                    |                | Females | Males      | Females | Males | Females | Males | Females | Males | Females | Males |
| CRP                                                                      | On admission       | mg/l           | 60.49 ± 1.35 | 90.54 ± 1.35 | 74.25 ± 1.35 | 95.36 ± 1.35 | 64.75 ± 1.35 | 87.45 ± 1.35 | 0.0674 | 0.69258 | N/A | N/A |
|                                                                          | On discharge       |                |            | 36.85 ± 0.36 | 58.33 ± 0.36 | 62.6 ± 0.36   | 86.23 ± 0.36 | 63.78 ± 0.36 | 90.42 ± 0.36 | <0.0001 | 0.0001 | 0.003 | 0.961 |
| Procalcitonin                                                           | On admission       | ng/ml          | 0.33 ± 0.57 | 1.24 ± 0.57 | 2.0 ± 0.57   | 1.53 ± 0.57 | 1.16 ± 0.57 | 0.86 ± 0.57  | 2.49 ± 0.57 | 1.11 ± 0.57 | 1.19 ± 0.57 | 0.5044 | 0.1807 |
|                                                                          | On discharge       |                |            | 0.57 ± 0.72 | 1.16 ± 0.72 | 1.37 ± 0.72   | 0.86 ± 0.72 | 2.49 ± 0.72 | 1.11 ± 0.72  | 1.19 ± 0.72 | 0.5044 | 0.1807 |
| IL-6                                                                    | On admission       | ng/ml          | 85.5 ± 3.52 | 45.2 ± 3.52 | 34.3 ± 3.52 | 59.9 ± 3.52 | 55.2 ± 3.52 | 69.2 ± 3.52 | 0.2692 | 0.2811 | N/A | N/A |
|                                                                          | On discharge       |                |            | 90.3 ± 4.03 | 672.0 ± 4.03 | 28.5 ± 4.03 | 56.5 ± 4.03 | 67.6 ± 4.03 | 82.3 ± 4.03 | 0.1877 | 0.1939 | N/A | N/A |
| D-dimer                                                                | On admission       | µg/ml          | 2.60 ± 0.15 | 4.63 ± 0.15 | 5.40 ± 0.15 | 7.84 ± 0.15 | 7.38 ± 0.15 | 11.48 ± 0.15 | 7.01 ± 0.15 | 0.0133 | 0.1192 | 0.501 | N/A |
|                                                                          | On discharge       |                |            | 3.17 ± 0.01 | 11.99 ± 0.01 | 4.38 ± 0.01 | 7.2 ± 0.01 | 6.85 ± 0.01 | 10.6 ± 0.01 | 0.3287 | 0.0215 | 0.016 | 0.821 |
| INR                                                                     | On admission       | µl/ml          | 1.07 ± 0.1 | 0.82–1.36 | 0.83–15.2 | 0.87–7.86 | 0.89–4.37 | 0.9–19.74 | 0.89–21 | <0.0001 | 0.0003 | 0.0002 | 0.136 |
|                                                                          | On discharge       |                |            | 1.1 ± 0.1 | 0.82–1.9 | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.32 ± 0.1 | 0.9–8.4 | 0.87–21.1 | 0.003 | 0.0019 | 0.048 | 0.114 |
| APTT                                                                    | On admission       | n/ml/100       | 6 ± 0.3 | 32 | 3 | 2 | 4 | 5 | 0.0243 | 0.5704 | 0.0337 | 0.107 | 0.1964 |
|                                                                          | On discharge       |                |            | 14 | 2.5 | 5 | 3 | 5 | 8 | 0.3472 | 0.2518 | N/A | N/A |
| Fibrinogen                                                              | On admission       | g/dl           | 4.69 ± 0.53 | 5.11 ± 0.53 | 4.34 ± 0.53 | 4.93 ± 0.53 | 3.62 ± 0.53 | 5.31 ± 0.53 | 0.0004 | 0.6765 | 0.441 | 0.0003 |
|                                                                          | On discharge       |                |            | 4.58 ± 0.48 | 4.95 ± 0.48 | 5.01 ± 0.48 | 4.98 ± 0.48 | 3.84 ± 0.48 | 5.71 ± 0.48 | 0.0184 | 0.2055 | 0.561 | 0.04 |

Continuous variables are presented as: mean ± SD; range (minimum—maximum) and number of 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. OMNIBUS, analysis of variance; N/A, non-applicable, a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red text—statistically significant values.
Table 5. Patient initial and on discharge laboratory assay in the studied cohort after C2HEST risk stratification.

| Parameter Time of Assessment | Units | Low Risk [0–1] | Medium [2–3] | High Risk [4–6] | p-Value OMNIBUS | p-Value for Post-Hoc Analysis |
|------------------------------|-------|----------------|-------------|-----------------|-----------------|-----------------------------|
|                              |       | Females | Males | Females | Males Biochemistry | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males |
| Glucose | mean ± SD/min-max/N | mg/dL | 128.1 ± 67.0 | 139.3 ± 79.5 | 144.1 ± 47.4 | 160.5 ± 74.9 | 131.3 ± 70.3 | 149.1 ± 86.5 | 152.0 ± 109.4 | 0.0035 | 0.0315 | 0.014 | 0.038 | 0.035 | 0.038 |
| On admission | | | 61.0-671.0 | 28.0-933.0 | 54.0-662.0 | 47.0-1026.0 | 70-685 | 120 | 104 | 0.035 | 0.038 | 0.038 | 0.038 |
| On discharge | | | 119.0 ± 56.0 | 127.3 ± 78.8 | 136.4 ± 58.0 | 150.7 ± 59.6 | 148.8 ± 54.0 | 143.5 ± 90.4 | 130.0 ± 106.4 | 0.0003 | 0.0012 | 0.004 | 0.005 | 0.003 | 0.005 |
| Glycated hemoglobin (HbA1c) | % | 7.1 ± 1.9 | 4.2-12.2 | 7.9 ± 2.5 | 4.9-14.9 | 7.2 ± 1.4 | 4.8-12.2 | 7.2 ± 1.7 | 5.1-11.4 | 0.3182 | 0.1497 | N/A | N/A |
| On admission | | | 35.1 | 35.8 | 40.6 | 50.6 | 47.5 | 48.9 | 57.1 | <0.001 | <0.001 | <0.001 | 0.197 | <0.001 | 0.042 |
| On discharge | | | 35.5 ± 29.6 | 32.9 | 59.0 ± 48.2 | 59.8 | 66.9 ± 41.7 | 88.9 ± 58.6 | 170-360.9 | N/A | N/A | 0.236 | 0.11 | N/A | N/A |
| Creatinine | mean ± SD/min-max/N | mg/dL | 1.0 ± 0.8 | 0.34-11.9 | 1.2 ± 0.9 | 0.48-9.56 | 1.58 ± 0.8 | 0.58-12.66 | 1.89 ± 1.27 | <0.001 | <0.001 | <0.001 | 0.008 | <0.001 | 0.002 |
| On admission | | | 353 | 683 | 275 | 203 | 130 | 137 | 0.16 | <0.001 | <0.001 | <0.001 | 0.026 | <0.001 | 0.002 |
| On discharge | | | 186 | 186 | 74 | 62 | 61 | 0.0235 | 0.0038 | N/A | N/A | N/A | 0.741 | N/A | N/A |
| Total protein | mean ± SD/min-max/N | g/L | 6.1 ± 3.9 | 6.1 ± 3.8 | 5.8 ± 3.6 | 6.0 ± 4.9 | 5.7 ± 3.8 | 5.7 ± 3.8 | 5.7 ± 3.8 | 0.0002 | 0.0012 | 0.002 | 0.003 | 0.002 | 0.003 |
| On admission | | | 145 | 145 | 78 | 78 | 62 | 61 | 0.741 | N/A | N/A | N/A | 0.741 | N/A | N/A |
| On discharge | | | 6.0 ± 3.9 | 3.8-8.1 | 6.0 ± 3.8 | 3.8-8.1 | 5.5 ± 3.8 | 3.8-8.1 | 5.7 ± 3.8 | 0.0002 | 0.0012 | 0.002 | 0.003 | 0.002 | 0.003 |
| Albumin | mean ± SD/min-max/N | g/L | 3.1 ± 1.6 | 3.2 ± 1.6 | 3.0 ± 1.6 | 3.2 ± 1.6 | 3.2 ± 1.6 | 3.2 ± 1.6 | 3.2 ± 1.6 | 0.0134 | 0.0307 | 0.001 | 0.018 | 0.007 | 0.018 |
| On admission | | | 152 | 152 | 78 | 82 | 62 | 67 | 0.307 | N/A | N/A | N/A | 0.307 | N/A | N/A |
| On discharge | | | 3.1 ± 1.6 | 1.4-4.6 | 3.0 ± 1.6 | 1.4-4.6 | 2.8 ± 0.5 | 1.4-3.7 | 2.8 ± 0.5 | 0.005 | 0.0049 | 0.004 | 0.004 | 0.004 | 0.004 |
| AST | mean ± SD/min-max/N | IU/L | 56.8 ± 39.7 | 62.7 ± 89.4 | 72.7 ± 343.6 | 58.8 ± 49.5 | 113.5 ± 450.8 | 102.8 ± 101.8 | 60.2 ± 101.8 | 0.3869 | 0.7844 | N/A | N/A |
| On admission | | | 6.0-2430.0 | 5.0-126.1 | 4.0-4776 | 7.0-323.0 | 8.0-3866.0 | 10.0-271.0 | 0.3869 | 0.7844 | N/A | N/A |
| On discharge | | | 123.4 ± 104.4 | 124.4 ± 104.4 | 70.2 ± 402.4 | 70.2 ± 402.4 | 97.4 ± 97.4 | 0.1438 | 0.5525 | N/A | N/A | N/A | N/A | N/A | N/A |
### Table 5. Cont.

| Parameter                          | Time of Assessment | Units | Low Risk [0–1] | Medium [2–3] | High Risk [4–4] | p-Value | p-Value for Post-Hoc Analysis |
|------------------------------------|-------------------|-------|----------------|--------------|----------------|---------|------------------------------|
| ALT                                | Mean ± SD/min-max/N | IU/L  | 47.0 ± 11.4 ± 52.2 ± 45.0 ± 57.1 ± 46.7 ± | 49.5 ± 10.6 ± 54.0 ± 57.8 ± 61.1 ± 57.4 ± | 58.9 ± 59.2 ± 62.1 ± 65.0 ± 68.7 ± 71.4 ± | 0.8212 | 0.0081 N/A 0.006<sup>a</sup> 0.026<sup>b</sup> 0.98<sup>c</sup> |
| On admission                       |                   |       | 435 537 219 172 | 435 537 219 172 | 435 537 219 172 |         |                              |
| On discharge                       |                   |       | 65 ± 105 ± 38.5 ± 61.1 ± 74.4 ± 71.4 ± | 60.6–5163.0 5.0–5499.0 7.0–6247.0 5.0–5995.0 9.0–1570.0 | 0.0624 | 0.6835 N/A N/A              |
| Bilirubin                          | Mean ± SD/min-max/N | mg/dL | 0.78 ± 0.88 ± 0.85 ± 0.80 ± 0.77 ± 0.98 ± | 0.60–767.0 1.0–29.0 2.0–9.0 3.0–3.1 0.4–0.6 4.0–8.0 | 0.5771 | 0.1292 N/A N/A              |
| On admission                       |                   |       | 363 489 195 157 | 363 489 195 157 | 363 489 195 157 |         |                              |
| On discharge                       |                   |       | 0.77 ± 0.95 ± 0.95 ± 0.76 ± 0.78 ± 1.06 ± | 0.1–19.0 0.1–25.9 0.2–35.3 0.2–3.1 0.3–6.1 0.2–12.8 | 0.6611 | 0.0224 N/A 0.123<sup>a</sup> 0.754<sup>b</sup> 0.08<sup>c</sup> |
| LDH                                | Mean ± SD/min-max/N | IU/L  | 404.5 ± 448.6 ± 368.2 ± 418.9 ± 468.1 ± 416.9 ± | 478.5 ± 198.6 ± 212.9 ± 1015.3 ± 269.7 ± | 0.3576 | 0.3427 N/A N/A              |
| On admission                       |                   |       | 304 519 1357 1172 | 304 519 1357 1172 | 304 519 1357 1172 |         |                              |
| On discharge                       |                   |       | 387.2 ± 398.2 ± 340.3 ± 407.1 ± 474.0 ± 387.8 ± | 794.3 ± 367.3 ± 243.5 ± 1028.1 ± 275.4 ± | 0.292 | 0.7848 N/A N/A              |
| Cardiac biomarkers                 |                   |       |                 |               |               |         |                              |
| BNP                                | Mean ± SD/min-max/N | pg/mL | 152.5 ± 254.1 ± 454.5 ± 433.3 ± 711.7 ± 1432.8 ± | 241.1 ± 782.4 ± 747.2 ± 995.6 ± 2864.5 ± | 0.0001 | 0.0526 <0.0001 0.054<sup>a</sup> 0.35<sup>a</sup> |
| On admission                       |                   |       | 54 107 50 50 | 54 107 50 50 | 54 107 50 50 |         |                              |
| On discharge                       |                   |       | 177.7 ± 239.8 ± 536.1 ± 396.2 ± 769.1 ± 2734.3 ± | 301.8 ± 566.2 ± 697.6 ± 225.3 ± 119.9 ± 119.9 ± | 0.0008 | 0.0206 0.0019 0.027<sup>b</sup> 0.082<sup>c</sup> |
| NT-proBNP                          | Mean ± SD/min-max/N | ng/mL | 1847 ± 2126.5 ± 6608.9 ± 1023.3 ± 14888.1 ± 13226.2 ± | 3250.7 ± 12708.7 ± 16141.4 ± 18982.5 ± 19276.7 ± | <0.0001 | <0.0001 0.015<sup>a</sup> 0.022<sup>a</sup> 0.003<sup>b</sup> |
| On admission                       |                   |       | 62 110 54 50 | 62 110 54 50 | 62 110 54 50 |         |                              |
| On discharge                       |                   |       | 1694 ± 1863.4 ± 7852.3 ± 10661.5 ± 13084.8 ± 12269.6 ± | 35000 ± 70000 ± 70000 ± 70000 ± 70000 ± 70000 ± | <0.0001 | <0.0001 0.016<sup>a</sup> 0.009<sup>a</sup> <0.0019<sup>c</sup> 0.267<sup>c</sup> 0.703<sup>c</sup> |
| Troponin I                         | Mean ± SD/min-max/N | ng/mL | 53 ± 211.1 ± 189.8 ± 768.3 ± 3044.2 ± 598.3 ± 542.7 ± | 53 ± 1015.9 ± 7215.3 ± 15465.9 ± 3316.8 ± 1724.6 ± | 0.015 | 0.0185 0.02<sup>b</sup> 0.867<sup>c</sup> 0.133<sup>b</sup> 0.156<sup>c</sup> |
| On admission                       |                   |       | 263 | 435 | 263 |         |                              |
| On discharge                       |                   |       | 105.7 ± 797.8 ± 692.7 ± 3359.3 ± 838.2 ± 493.1 ± | 873.1 ± 2743.6 ± 18244.2 ± 3666.2 ± 1504.8 ± | 0.0977 | 0.0095 N/A 0.104<sup>a</sup> 0.055<sup>b</sup> 0.17<sup>c</sup> |
| n/m (%)<sup>a</sup>/N = F >3-fold | Mean ± SD/min-max/N | mg/dL | 106.8 ± 96.2 ± 93.9 ± 79.4 ± 83.3 ± 64.2 ± | 64.8 ± 40.6 ± 39.7 ± 40.6 ± 44.2 ± 37.6 ± | 0.0498 | 0.0013 0.028<sup>a</sup> <0.0001<sup>b</sup> 0.037<sup>a</sup> 0.0017<sup>c</sup> 0.0019<sup>c</sup> 1.0<sup>c</sup> |
| LDL cholesterol                    | Mean ± SD/min-max/N | mg/dL | 85 147 69 60 | 85 147 69 60 | 85 147 69 60 |         |                              |
| On admission                       |                   |       | 85 147 69 60 | 85 147 69 60 | 85 147 69 60 |         |                              |
### Table 5. Cont.

| Parameter Time of Assessment | Units | Low Risk [0–1] | Medium [2–3] | High Risk [≥ 4] | p-Value OMNIBUS | p-Value for Post-Hoc Analysis |
|-----------------------------|-------|----------------|--------------|----------------|-----------------|-----------------------------|
|                            |       | Females | Males | Females | Males | Females | Males | Females | Males | Females | Males |
| HDL-cholesterol | mean ± SD/min-max/N | mg/dL | | | | | | | | | | |
| On admission | 199.4 ± 154.5 | 173.7 ± 105.1 | 141.0 ± 94.5 | 148.0 ± 98.8 | 133.4 ± 56.7 | 124.8 ± 66.9 | 0.0022 | 0.0001 | 0.016 | 0.001 | <0.0001 | 0.117 |
| Triglycerides | mean ± SD/min-max/N | mg/dL | | | | | | | | | | |
| On admission | 27.4 ± 21.8 | 23.4 ± 15.0 | 26.1 ± 17.2 | 22.9 ± 15.4 | 22.4 ± 16.8 | 14.5 ± 9.6 | 0.3738 | 0.0006 | N/A | 0.0018 | 0.036 |
| 25-hydroxy-vitamin D | mean ± SD/min-max/N | ng/mL | | | | | | | | | | |
| On admission | 1.55 ± 0.03–1.86 | 1.2 ± 0.00–1.06 | 1.72 ± 2.98 | 1.31 ± 1.39 | 2.74 ± 0.3 ± 0.54 | 1.25 ± 1.06 | 0.1063 | 0.3834 | N/A | N/A |
| TSH | mean ± SD/min-max/N | mIU/L | | | | | | | | | | |
| On admission | 0.21 ± 0.00–0.07 | 0.00–0.05 | 0.21 ± 0.01 | 0.10 ± 0.01 | 0.30 ± 0.00–0.05 | 0.10 | 0.05 | 0.05 | 0.0001 | 0.0001 | 0.0001 |

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. OMNIBUS, analysis of variance; N/A, non-applicable, a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red text = statistically significant values.

Both genders revealed significant differences between the C2HEST strata and complete blood count parameters along with ion parameters. Noteworthy, no significant differences between strata in terms of initial inflammatory markers (procalcitonin, IL-6, CRP) along with acid-base balance parameters were noted.

The parameters of kidney function, including urea, creatinine, eGFR maintained significantly worse in the high-risk C2HEST stratum for both genders, however baseline serum concentration of protein and albumin was significantly lower only in females with higher C2HEST score value. In both study cohorts we observed increasing level of cardiac injury markers including troponin T and NT-pro-BNP levels in patientsallocated higher-risk group depending on their C2HEST score value. Surprisingly, lipid disorders (level of LDL and triglycerides) noticed at the time of admission were less severe subjects from high-risk stratum in both study cohorts.

#### 3.2. Specific Treatment Applied during Hospitalization

Differences in applied treatment during hospitalization between the C2HEST group among genders are highlighted in Table 6. Women in the higher C2HEST stratum were prone to receive convalescent plasma. We did not observe any differences among the male cohort. In both study arms, we observed changes in the prevalence of antibiotic application. Subjects from the high-risk stratum more often received this type of therapy.

The assignment to specific C2HEST stratum score correlated with the type of respiratory support applied during the hospitalization. Additionally, in the male cohort, it correlated with the prevalence of coronary revascularization procedures during index hospitalization along with the need for the catecholamine’s administration (Table 7).
Table 6. Treatment applied during hospitalization.

| Variables, Units | Low Risk [0–1] | Medium [2–3] | High Risk [≥4] | p-Value OMNIBUS | p-Value for Post-Hoc Analysis |
|------------------|----------------|--------------|----------------|----------------|-----------------------------|
|                  | Females N = 681 | Males N = 735 | Females N = 284 | Males N = 207 | Females N = 135 | Males N = 139 | Females N = 135 | Males N = 139 |
| Applied treatment and procedures | | | | | | | | |
| Systemic corticosteroid n/m%(%) | 299 (43.8) | 409 (55.6) | 127 (44.7) | 119 (57.2) | 64 (47.4) | 78 (56.1) | 0.7456 | 0.9222 |
| Convalescentplasma n/m%(%) | 54 (7.9) | 113 (15.4) | 12 (4.2) | 29 (13.9) | 15 (11.1) | 16 (11.5) | 0.0274 | 0.4749 |
| Tocilizumab n/m%(%) | 11 (1.6) | 11 (1.5) | 0 (0.0) | 2 (1.0) | 1 (0.7) | 0 (0.0) | 0.054 | 0.4308 |
| Remdesivir n/m%(%) | 81 (12.2) | 153 (20.8) | 47 (16.8) | 35 (16.8) | 12 (8.9) | 45 (16.5) | 0.4627 | 0.2822 |
| Antibiotic n/m%(%) | 338 (49.6) | 408 (55.5) | 157 (55.3) | 146 (70.2) | 88 (65.2) | 103 (74.1) | 0.0026 | <0.0001 |

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; OMNIBUS, analysis of variance; N/A, non-applicable; a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red text = statistically significant values.

Table 7. Applied treatment and procedures.

| Variables | Low Risk [0–1] | Medium [2–3] | High Risk [≥4] | p-Value OMNIBUS | p-Value for Post-Hoc Analysis |
|-----------|----------------|--------------|----------------|----------------|-----------------------------|
|           | Females N = 681 | Males N = 735 | Females N = 284 | Males N = 207 | Females N = 135 | Males N = 139 | Females N = 135 | Males N = 139 |
| The most advanced respiratory support applied during the hospitalisation no oxygen n/m%(%) | 409 (60.1) | 332 (45.2) | 140 (49.3) | 62 (30.0) | 50 (37.0) | 39 (28.1) | <0.0001 | <0.0001 |
| low flow oxygen support n/m%(%) | 199 (29.2) | 252 (34.3) | 103 (36.3) | 85 (41.1) | 65 (48.1) | 59 (42.4) | <0.0001 | <0.0001 |
| high flow nasal cannula n/m%(%) | 26 (3.8) | 56 (7.6) | 24 (8.5) | 28 (13.5) | 17 (12.6) | 22 (15.8) | <0.0001 | 0.0114 |
| invasive ventilation n/m%(%) | 47 (6.9) | 94 (12.8) | 17 (6.0) | 32 (15.5) | 3 (2.2) | 19 (13.7) | <0.0001 | 0.0021 |
| Oxygenation parameters from the period of qualification for advanced respiratory support: SpO₂%, mean ± SD/(min-max/N) | 92.2 ± 6.8 | 88.8 ± 8.6 | 87.0 ± 11.0 | 86.0 ± 8.4 | 86.2 ± 9.3 | 85.1 ± 11.0 | <0.0001 | 0.0159 |
| Therapy with catecholamines n/m%(%) | 39 (5.7) | 92 (12.5) | 14 (4.9) | 31 (14.9) | 9 (6.7) | 33 (23.7) | 0.7614 | 0.0025 |
| Coronary revascularisation un/and an indication for coronary revascularisation, n/m%(%) | 1 (0.1) | 7 (1.0) | 3 (1.1) | 8 (3.8) | 1 (0.7) | 6 (4.3) | 0.0795 | 0.0021 |
| Haemodialysis n/m%(%) | 15 (2.2) | 31 (4.2) | 2 (0.7) | 11 (0.7) | 4 (3.0) | 8 (5.8) | 0.1486 | 0.6417 |

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; OMNIBUS, analysis of variance/N/A, non-applicable; a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red text = statistically significant values.

3.3. Association C₂HEST Score with Results and Mortality

In the female cohort, the in-hospital and three-month and six-month mortality rates were the highest in high-risk C₂HEST stratum reaching 31.9%, 48.1%, and 61.4%. Noteworthy, mortality rates in the medium-risk stratum were significantly higher than in low-risk. All data regarding short and long-term mortality were presented in Table 8. Similarly, in the males’ cohort in-hospital, three-month and six-month mortality was also highest in the
**high-risk** C₂HEST stratum and come to 38.8%, 59.0%, and 68.8%. Also, in this study arm differences between all C₂HEST groups were statistically significant.

**Table 8.** Total and in-hospital all-cause mortality in the C₂HEST risk strata in males’ and females’ cohort.

| Variables                        | Low Risk [0–1] | Medium [2–3] | High Risk [≥4] | p Value OMNIBUS | p Value for Post-Hoc Analysis |
|----------------------------------|----------------|--------------|----------------|----------------|-------------------------------|
|                                   | Females N = 682| Males N = 735| Females N = 284| Males N = 208   | Females N = 135               | Males N = 139               | Females | Males | Females | Males |
| **In-hospital mortality n/n(%)** |                |              |                |                |                               |                             |         |       |         |       |
| 3-month mortality n/n(%)         |                |              |                |                |                               |                             |         |       |         |       |
| Females                          | 36 (5.3)       | 83 (11.3)    | 50 (17.6)      | 60 (28.8)      | 43 (31.9)                   | 54 (38.8)                   | <0.0001 | <0.0001| <0.0001| <0.0001|
| Males                            | (10.0)         | (18.2)       | (33.5)         | (49.5)         | (48.1)                      | (59.0)                      | <0.0001 | <0.0001| <0.0001| <0.0001|
| **6-month mortality n/n(%)**     |                |              |                |                |                               |                             |         |       |         |       |
| Females                          | 72 (17.3)      | 142 (31.4)   | 104 (49.3)     | 104 (60.1)     | 70 (61.4)                   | 86 (68.8)                   | <0.0001 | <0.0001| <0.0001| <0.0001|
| Males                            | 415 (12.9)     | 452 (12.1)   | 211 (173)      | 114 (125)      | <0.0001                     | <0.0001                     | 0.1454  | 0.4696 | <0.0001| <0.0001|

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; OMNIBUS, analysis of variance; N/A, non-applicable; a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red text = statistically significant values.

3.4. The All-Cause Mortality Discriminatory Performance of the C₂HEST Score

The time dependent receiver operating characteristic (ROC) analysis in both study cohorts revealed that the C₂HEST scale is more sensitive in the female cohort (Figure 1). The C₂HEST predicting AUC in women vs. man cohorts were higher at all calculated periods. Following the 1-month AUC = 72.5 vs. 70.3% 3-month AUC = 74.6 vs. 71.3%, six-month AUC = 73.8 vs. 68.4%. All of the data were calculated for all-cause death without competing risk Figure 2 present ROC analysis in the male population. Figure 3 presented the time-dependent AUC for the C₂HEST score in predicting the all-cause deaths in both cohort, slightly higher AUC value was observed in the female arm. The survival curves for the C₂HEST stratum in both study cohorts were estimated using Kaplan-Meier functions. The p value for Log-rank test was <0.0001 (Figure 4). We have observed differences in estimated survival probability in both study cohorts. Practically, starting from admission time, the females were more likely to survive the COVID-19. Estimated six-month survival probability for high-risk subjects reached 0.5 in the female cohort, while for the male subject was below 0.4. Similarly, in medium-risk-stratum for women the survival probability was above 0.6 when compared to 0.5 in men. Additionally, the low-risk subjects in the female cohort maintained at the level of more than 0.9 for the whole observation period while in men reached 0.8, respectively.
Figure 1. The time dependent receiver operating characteristic (ROC) for all-cause mortality in female cohort.

Figure 2. The time dependent receiver operating characteristic (ROC) for all-cause mortality in male cohort.
Figure 3. Time-dependent ROC analysis for the C2HEST predictive abilities of all cause death in both study cohorts.

Figure 4. The survival curves for the C2HEST stratum in both study cohorts estimated by Kaplan-Meier function.

Subsequently, two Cox models were analyzed to assess the effect of the C2HEST score stratification on COVID-19 mortality. The overall model takes an uncategorized value of the C2HEST score, and it met the hazard proportional assumption in both study cohorts. An additional point in the C2HEST score resulted in increased the total-death intensity approximately in 42.8% in female subjects (HR 1.428, 95% CI 1.349–1.513 p < 0.0001) and respectively in male population 40.0% (HR 1.400, 95% CI 1.331–1.474 p < 0.0001). Furthermore, considering the categorized model, the change from the low to the medium category in the female population increased death expectation 4.267 times, and respectively; 3.289 times for males. Subsequently, transfer between the low-risk stratum to high-risk stratum raised all-cause death intensity 6.52 (female) and 4.476(male) times. The data are shown in Tables 9 and 10.

Table 9. The total all-cause-death hazard Ratios for C2HEST risk stratification in female cohort.

| Overall | HR          | 95% CI        | p Value |
|---------|-------------|---------------|---------|
| Overall | 1.428       | 1.349–1.513   | <0.0001 |
| Risk strata |          |               |         |
| Low risk vs. Medium risk | 4.267       | 3.170–5.732   | <0.0001 |
| Low risk vs. High risk | 6.524       | 4.714–9.031   | <0.0001 |

Red text—statistically significant values.
Table 10. The total all-cause-death Hazard Ratios for C₂HEST risk stratification in male cohort.

| Total Death | HR     | 95%CI   | p Value |
|-------------|--------|---------|---------|
| Overall     | 1.400  | 1.331–1.474 | <0.0001 |

| Risk strata | HR     | 95%CI   | p Value |
|-------------|--------|---------|---------|
| Low risk vs. Medium risk | 3.289  | 2.559–4.227 | <0.0001 |
| Low risk vs. High risk    | 4.476  | 3.438–5.827 | <0.0001 |

Red text = statistically significant values.

The associations of individual C₂HEST score components with mortality in both study cohorts are presented in Tables 11 and 12. The highest prognostic value for all-cause death in both study groups was noticed for age (in women 2.750 vs. 3.059 in men, respectively). Interestingly, coronary artery disease was associated with higher HR for death only in men, whereas the COPD and hypertension only in woman.

Table 11. Associations of individual C₂HEST score components with mortality in female cohort.

| Component            | HR     | CI Min. | CI Max. | p Value |
|----------------------|--------|---------|---------|---------|
| All-cause mortality  |        |         |         |         |
| Coronary artery disease | 1.133  | 0.743   | 1.728   | 0.5627  |
| COPD                 | 2.083  | 1.299   | 3.532   | 0.0064  |
| Age > 75             | 2.750  | 2.088   | 3.6216  | <0.0001 |
| Thyroid disease      | 0.784  | 0.566   | 1.105   | 0.1649  |
| Hypertension         | 1.881  | 1.394   | 2.537   | <0.0001 |
| HfrEF                | 1.584  | 1.134   | 2.212   | 0.007   |

Abbreviations: COPD, chronic obstructive pulmonary disease; HfrEF, heart failure with reduced ejection fraction. Red text = statistically significant values.

Table 12. Associations of individual C₂HEST score components with mortality in male cohort.

| Component            | HR     | CI Min. | CI Max. | p Value |
|----------------------|--------|---------|---------|---------|
| All-cause mortality  |        |         |         |         |
| Coronary artery disease | 1.568  | 1.180   | 2.084   | 0.0019  |
| COPD                 | 1.182  | 0.786   | 1.615   | 0.4227  |
| Age > 75             | 3.0541 | 2.411   | 3.869   | <0.0001 |
| Thyroid disease      | 1.126  | 0.688   | 1.842   | 0.6378  |
| Hypertension         | 1.200  | 0.952   | 1.513   | 0.1233  |
| HfrEF                | 1.415  | 1.055   | 1.899   | 0.0206  |

Abbreviations: COPD, chronic obstructive pulmonary disease; HfrEF, heart failure with reduced ejection fraction. Red text = statistically significant values.

Additionally, we verified whether the original cut-off values for particular C₂HEST score risk (the low/medium/high-risk categories for 0–1/2–3/≥4 points, respectively) is potentially the best possible stratification system. Regarding the difference in Kaplan-Meier survival curves, all of the possible C₂HEST intervals were analyzed in both study cohorts, and for each, we calculated the log-rank statistics (Tables 13 and 14). The highest value of log-rank test statistics, presenting the best cut-off point for high (h) and medium (m) strata was obtained for the original C₂HEST-score risk strata in the female population (m2 and h4, respectively). On the other hand, in male cohort the highest value of the Log-rank corresponded with m2 and h5, which reflects the following strata: 0–1 low, 2–4 medium, 5–8 high.
Table 13. The log-rank statistics for matching the C2HEST risk strata for in-hospital mortality in female cohort.

|    | H2   | h3  | h4   | h5   | h6   | h7   | h8   |
|----|------|-----|------|------|------|------|------|
| m1 | 164.317 | 148.669 | 142.661 | 121.294 | 105.396 | 105.533 | 10.259 |
| m2 | 158.373 | 166.213 | 158.483 | 155.603 | 155.940 | 12.436 |
| m3 | 122.464 | 116.484 | 116.367 | 116.190 | 10.699 |
| m4 | 79.813 | 86.505 | 82.846 | 8.919 |
| m5 | 45.423 | 40.946 | 6.156 |
| m6 | 3.820 | 1.793 |
| m7 | 0.139 |

Abbreviations: m, medium; h, high. Red text = statistically significant values.

Table 14. The Log-rank statistics for matching the C2HEST risk strata for in-hospital mortality in male cohort.

|    | H2   | h3  | h4   | h5   | h6   | h7   | h8   |
|----|------|-----|------|------|------|------|------|
| m1 | 152.361 | 134.106 | 118.904 | 112.785 | 98.649 | 84.149 | 8.929 |
| m2 | 152.619 | 154.813 | 159.181 | 155.352 | 149.997 | 12.183 |
| m3 | 116.694 | 121.473 | 118.900 | 115.004 | 10.673 |
| m4 | 84.079 | 82.389 | 79.865 | 8.909 |
| m5 | 58.586 | 58.244 | 7.628 |
| m6 | 32.326 | 5.686 |
| m7 | 2.769 |

Abbreviations: m, medium; h, high. Red text = statistically significant values.

3.5. Relationship of C2HEST Score with Non-Fatal Outcomes

Clinical non-fatal events in the C2HEST risk strata in both study arms are presented in Table 15. In both study cohorts, the subjects assigned to the C2HEST high-risk stratum were characterized by greater prevalence of pneumonia, acute kidney injury, and cardiovascular disorders during hospitalization. This observation regards myocardial injury, myocardial infarction, acute heart failure, and cardiogenic shock. Additional, female subjects with higher C2HEST values were more prone to subject a new episode of stroke/transient ischemic attack (TIA), and systemic inflammatory response syndrome (SIRS) during hospitalization. On the other hand, a high C2HEST score in the male subpopulation was associated with a higher probability of shock, acute liver dysfunction, and bleeding occurrence.

Table 15. Clinical non-fatal events in the C2HEST risk strata in both study arms.
### Table 15. Cont.

| Variables | Low Risk | Medium Risk | High Risk | p-Value Omnibus | p-Value for Post-Hoc Analysis |
|-----------|----------|-------------|-----------|----------------|-------------------------------|
|           | Females  | Males       | Females  | Males          | Females | Males | Females | Males |
| Myocardial infarction | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0251 | 0.0038 | 0.004 b | 0.0058 b |
| n/n (%)   | (2.8)    | (2.1)      | (1.1)    | (3.4)         | (2.2)   | (3.6)   |           |           |        |        | 1.0 c    | 1.0 c    |
| Myocardial injury, 3x, n/subject/N | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0194 | <0.0001 | 0.0017 c | <0.0001 ab |
| n/n (%)   | (17.5)   | (16.1)     | (29.8)   | (35.1)        | (52.1)  | (39.2)  |           |           |        |        | 1.0 c    | 1.0 c    |
| Acute heart failure | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | <0.0001 | <0.0001 |            |           |
| n/n (%)   | (0.7)    | (0.4)      | (2.8)    | (6.7)         | (17.8)  | (15.8)  |           |           |        |        |          |          |
| Stroke/TIA | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0002 | 0.4167 | 0.0006 c | 0.0872 b |
| n/n (%)   | (0.6)    | (1.9)      | (4.2)    | (3.4)         | (3.0)   | (2.2)   |           |           |        |        | 1.0 c    | N/A      |
| Pneumonia | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | <0.0001 | 0.0004 | <0.0001 ab | 0.5343 c |
| n/subject/N | (39.3) | (56.3) | (57.4) | (67.8) | (65.2) | (70.5) |           |           |        |        | 1.0 c    | 0.0076 b |
| Complete respiratory failure | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.2528 | 0.1348 | N/A | N/A |
| n/subject/N | (47.9) | (46.6) | (43.2) | (58.8) | (62.5) | (65.7) |           |           |        |        |          |          |
| SIRS      | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0158 | 0.4818 | 0.0034 b | 0.0636 c |
| n/subject/N | (8.2)  | (12.6) | (7.8)  | (9.7)  | (15.7) | (10.8) |           |           |        |        | 1.0 c    | N/A      |
| Sepsis    | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0777 a | <0.0001 b | 0.0019 a | <0.0001 ab |
| n/subject/N | (5.4)  | (9.9) | (10.6) | (17.8) | (20.7) | (22.3) |           |           |        |        | 1.0 c    | 1.0 c    |
| Acute kidney injury | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | <0.0001 | <0.0001 | 0.0194 a | 0.0003 b |
| n/subject/N | (1.9)  | (2.9) | (4.5)  | (5.1)  | (4.0)  | (7.1)  |           |           |        |        | 1.0 c    | 1.0 c    |
| Acute liver dysfunction | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0619 | 0.0458 | N/A | N/A |
| n/subject/N | (1.0)  | (1.9) | (1.1)  | (2.4)  | (3.0)  | (2.9)  |           |           |        |        | 0.5214 c | 0.0956 b |
| Multiple organ dysfunction syndrome | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.0001 | 0.0117 a | 0.0076 b | 0.0019 c |
| n/subject/N | (7.0)  | (5.0) | (4.6)  | (5.8)  | (6.7)  | (11.5) |           |           |        |        | 1.0 c    | 1.0 c    |
| Bleedings | N = 682 | N = 735 | N = 284 | N = 208 | N = 135 | N = 139 |           |           | 0.3758 | 0.0128 | 0.0117 a | 0.0184 b |
| n/subject/N | (27.0) | (40.0) | (37.0) | (34.0) | (26.0) | (24.0) |           |           |        |        | 0.2545 c |          |

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. Abbreviations: N, valid measurements; n, number of patients with parameter above cut-off point; SD, standard deviation; OMNIBUS, analysis of variance; TIA, transient ischemic attack; SIRS, systemic inflammatory response syndrome; N/A, non-applicable; a low risk vs. medium risk, b low risk vs. high risk, c medium risk vs. high risk. Red color text = statistically significant values.

Additionally, the overall odds ratio for the discriminatory performance of the C2HEST score on the clinical non-fatal events was summarized in Figure 5 (female) and Figure 6 (male). Noteworthy, the highest predictive of C2HEST score value in the female cohort was achieved for, acute heart failure (OR_{overall} = 2.180, 95%CI 1.778–2.724, p = 0.0034). Similar findings were observed in the male cohort -the highest value was observed for acute heart failure (OR_{overall} = 1.861, 95%CI 1.574–2.229, p < 0.0001).
Figure 5. The overall odds ratio for the discriminatory performance of the C2HEST score on the clinical non-fatal events in female cohort. Abbreviations: MODS, multiple organ dysfunction syndrome; TIA, transient ischemic attack; SIRS, systemic inflammatory response syndrome. Significance code: * <0.05; ** <0.01; *** <0.001; **** <0.0001.

Figure 6. The overall odds ratio for the discriminatory performance of the C2HEST score on the clinical non-fatal events in female cohort. Abbreviations: MODS, multiple organ dysfunction syndrome; TIA, transient ischemic attack; SIRS, systemic inflammatory response syndrome. Significance code: * <0.05; ** <0.01; *** <0.001; **** <0.0001.
4. Discussion

Several studies demonstrated [11] no significant differences regarding the susceptibility to the SARS-CoV-2 infection between biological genders. Nevertheless, male gender is an independent risk factor for the poor outcome of COVID-19 including higher severity and fatality rates [12]. Various biological factors may play a role in sex-dependent different responses to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Biological sex affects the initial phase of infection mainly by sex-based differences in the expression of the ACE2 receptor responsible for the entry of the SARS-CoV-2 into the cells [13]. Sex differences affect also an immune response to viral infection. Females tend to have a lower potency to develop an uncontrolled inflammatory response process [14] with coexisting decreased viral load during the infection. The physiological mechanism of this process is multifactorial [15,16] and includes the sex-specific transcriptional regulatory network, various gen variants especially connected with chromosome X, epigenetic modifications, transcription factors, and sex steroids. Noteworthy, different social, behavioral, and comorbid factors are also postulated [17] to worsen the prognosis in men.

The previously observed sex-dependent dichotomy in the COVID-19 mortality was also confirmed in our study. For all of the three C2HEST strata, greater fatality rate in the male cohort compared to the female one was noted. Independently, we confirmed the previously reported usefulness of the C2HEST score in predicting the adverse COVID-19 outcomes, including the mortality in both genders. However, despite lower mortality observed in women, the ROC analysis revealed that the C2HEST-score is a more sensitive tool in women regarding the short- and mid-term (up to 6 month-) mortality (for 1-month the AUC = 72.5 vs. 70.3% and for 6-month AUC = 73.8 vs. 68.4 % in men, respectively). Gender is often considered among the variables defining the probability of a severe clinical outcome of infection.

Analysis of individual C2HEST score variables in both cohorts revealed differences between gender in features significantly affecting mortality. Beyond age and previously diagnosed heart failure common for both sexes, in the female group, only hypertension and COPD reached statistical significance. On the other hand, in the male cohort such observation was made for coronary artery disease. Although the pathophysiology underlying severe COVID-19 course remains not fully understood, it can be hypothesized that endothelial dysfunction induced by hypertension [18] might abolish the initial favorable female immune response [14] to SARS-CoV-2 infection. Moreover, the endothelial dysfunction promotes microvascular thrombi and pro-thrombotic state associated with respiratory failure and fatal outcome in COVID-19 [19]. On the other hand, the increased mortality rate of COVID-19 male patients with CAD is probably related to the presence of multiple comorbidities [20] or direct myocardial injury connected with enhanced platelet activation induced by SARS-CoV-2 infection [21].

It is noteworthy that, besides observed in both genders significant differences in mortality between the C2HEST strata, a similar relationship was noticed in the prevalence of pneumonia and cardiovascular non-fatal secondary outcomes (myocardial infarction, myocardial injury, acute heart failure, cardiogenic shock, and acute kidney failure). Our study revealed that in the male cohort alongside with higher C2HEST stratum, a greater rate of acute liver injury (ALI), bleedings and shock was present. This observation supports the previously described relationships between male gender and liver impairment in COVID subjects [22]. Although the mechanism of liver injury in SARS-CoV-2 infection remains unclear, a combination of direct viral inclusion of hepatocytes, as well as the result of uncontrolled immune, may be responsible for the damage, which interestingly, have also been associated with poor outcomes in COVID patients [23].

Furthermore, some data [5,24] suggests that individuals with gastrointestinal problems particularly those with earlier stages of liver impairment are more prone to develop severe COVID-19 disease with advanced respiratory failure. Concerning epidemiological data a higher prevalence of liver disorders [25] with coexisting higher susceptibility for endothelial dysfunction [26,27] may be important factors affecting outcomes in the male population.
It is possible that acute liver injury in the male cohort may be also partially responsible for the higher rate of bleedings as a result of coagulation systems disorders (mild elevations of INR, activated partial thromboplastin time (APTT), and thrombin time (TT)) observed in patients with ALI in course of COVID-19 [23,28]. Initial higher level of INR in males high-risk C2HEST score stratum seems to support this thesis. Although the principal clinical manifestation of severe COVID-19 is a respiratory failure with a coexisting uncontrolled immune reaction, subjects with COVID-19 show a high incidence of thromboembolic events [29], particularly in fatal cases [30], however antithrombotic treatment prior to COVID-19 infection is unlikely to have a protective effect [31]. Bleeding complications in subjects with COVID-19 give rise to justifiable concerns [32,33] and should always be considered before applying anticoagulation in patients with SARS-CoV-2 infection. Therefore several predictive scores [34] focused on identifying patients at increased risk for major bleeding have been recently proposed. Results of our study suggest that the C2HEST score might be also useful in the identification of the “high-risk for bleeding” subpopulations. However, subsequent studies are needed to define predictive value of the C2HEST score in terms of bleedings.

Limitations

We have observed several limitations of this study including the retrospective, single-center, character. These factors could affect the validity of our conclusions. Additionally, the study population was homogeneous and consisted of hospitalized patients and not involved ambulatory subjects. Furthermore, all hospitalizations were carried out in the face of limited resources (global COVID-19 pandemic) probably these extraordinary circumstances could partially affect the clinical outcomes.

5. Conclusions

To the best of our knowledge, this study is the first demonstration of the sex-dependent differences in the predictive value of the C2HEST score in subjects admitted to hospital due to SARS-CoV-2 infection. This simple risk score evaluated during the hospital admission could predict adverse outcomes in both including in-hospital and six-month-mortality and other clinical events such as acute kidney injury, myocardial injury acute heart failure, myocardial infarction, and cardiogenic shock. Additionally in the male cohort, it well correlated with acute liver injury and prevalence of all kinds of bleeding. The simplicity of this scale allows assuming that C2HEST-score might become a useful triage tool for risk stratification in both genders with COVID-19.

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