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## ORIGINAL ARTICLE

# D-Dimer Levels and the Risk of 30-Day All-Cause Mortality in Cardiogenic Shock Stratified by Etiology

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## SUMMARY

***Background:*** **The study investigates the prognostic impact of D-dimer levels in patients with cardiogenic shock (CS). Although D-dimer levels were found to be associated with prognosis in various clinical settings such as heart failure or acute myocardial infarction (AMI), the prognostic role of D-dimer levels in CS patients has not yet been clarified.**
***Methods:*** **Consecutive CS patients with and without concomitant AMI were prospectively included from 2019 to 2021. The prognostic impact of D-dimer levels was tested for 30-day all-cause mortality within the entire study cohort and stratified by the presence or absence of AMI. Statistical analyses included C-statistics, Kaplan-Meier, and multivariate Cox regression analyses.**
***Results:*** **One hundred and twenty-three consecutive CS patients were included with an overall all-cause mortality at 30 days of 55%. The median D-dimer level on admission was 8.44 mg/L, whereas D-dimer levels were higher in 30-day non-survivors compared to survivors (median 13.0 vs. 5.2 mg/L; p = 0.011). D-dimer levels above the median were associated with an increased risk of 30-day all-cause mortality compared to patients with lower D-dimer levels (66% vs. 54%, log rank p = 0.050; HR = 1.594; 95% CI 0.979 - 2.594; p = 0.061), especially in patients with non-AMI-related CS (65% vs. 30%, log rank p = 0.010). The prognostic value of D-dimer levels was still demonstrated after multivariate adjustment (HR = 1.024; 95% CI 1.004 - 1.045; p = 0.020).**
***Conclusions:*** **D-dimer measurement may be a reliable biomarker to predict the risk of 30-day mortality in CS patients, especially in patients with non-AMI related CS.**
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**KEYWORDS**

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## INTRODUCTION

Cardiogenic shock (CS) is characterized by cardiac pump failure resulting into hypoperfusion and tissue hypoxia [1]. Despite the investigation of multiple treat-

ment strategies in CS, including the use of different mechanical circulatory support (MCS) devices, CS-related 30-day mortality rates remain high at approximately 50% [2,3]. During the past years, characteristics and presentation of CS patients has significantly changed. Whereas the rates of CS related to acute myocardial infarction (AMI) were shown to decrease as a result of shorter door-to-balloon times, coronary revascularization strategies, and pharmacotherapies, especially the rates of non-AMI related CS, mainly attributed to acute decompensated heart failure (ADHF) were shown to increase [4]. This may be related to demographic changes and the overall improved treatment strategies for patients with cardiovascular diseases leading to a large proportion of patients with advanced stages of heart failure. Those patients represent a profound different study cohort, typically characterized by non-shockable rhythm in the setting of cardiopulmonary resuscitation (CPR) as an expression of end-stage heart failure. In line, mortality rates following ADHF-related CS were shown to increase during the past years [5].

Due to the overall high mortality rates, risk stratification in CS patients is complex and as yet limited data regarding the prognostic value of blood-derived biomarkers is available. For instance, serum creatinine, hemoglobin, serum lactate, blood glucose, and N-terminal pro-brain natriuretic peptide (NT-proBNP) were identified to predict the risk of all-cause mortality following CS [6,7].

D-dimer, a specific product of degradation of fibrin clots, may be increased as a consequence of various clinical conditions including pulmonary embolism (PE), cancer, sepsis, and following surgery, but also in patients with ischemic cardiomyopathy and congestive heart failure [8,9]. In patients with stable coronary artery disease and in AMI patients, high D-dimer levels were shown to indicate poor long-term prognosis [10]. However, within studies investigating AMI patients, the rate of concomitant CS varies from 5 to 8%, whereas no sub-studies focusing on the prognostic impact of D-dimer levels in patients with CS are as yet available [4,11].

Therefore, the present study investigates the prognostic impact of D-dimer levels on the risk of 30-day all-cause mortality in consecutive CS patients treated at an internistic intensive care unit (ICU).

## MATERIALS AND METHODS

### Study patients, design, and data collection

The present study prospectively included all consecutive patients presenting with CS on admission to the internistic ICU at the University Medical Center Mannheim, Germany, from June 2019 to May 2021, as recently published [12,13]. All relevant clinical data related to the index event were documented using the electronic hospital information system as well as the IntelliSpace Critical Care and anesthesia information system (ICCA, Philips, Philips GmbH Market DACH, Hamburg, Germany) implemented at the ICU, organizing patient data such as admission documents, vital signs, laboratory values, treatment data and consult notes. Important laboratory data, ICU-related scores, hemodynamic measurements, ventilation parameters were assessed on the day of admission (i.e., day 1), as well as on day 2, 3, 4, and 8. Furthermore, baseline characteristics, prior medical history, length of index hospital stay, data derived from imaging diagnostics, as well as pharmacological therapies were documented. Documentation of source data was performed by intensivists and ICU nurses during routine clinical care.

The present study derived from an analysis of the "Cardiogenic Shock Registry Mannheim" (CARESMA-registry), representing a prospective single-center registry including consecutive patients presenting with cardiogenic shock being acutely admitted to the ICU for internal medicine of the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT05575856). The registry was carried out according to the principles of the Declaration of Helsinki and was approved by the medical ethics committee II of the Medical Faculty Mannheim, University of Heidelberg, Germany.

### Inclusion and exclusion criteria, study endpoints

For the present study, all consecutive patients with CS treated at one internistic ICU were included. Patients with no measurement of D-dimer levels within 48 hours of admission were excluded. In patients with multiple D-dimer measurement within 48 hours, the highest D-dimer level was considered. Further exclusion criteria comprised CS related to pulmonary embolism and aortic dissection, since D-dimer levels were shown to increase in these settings (Figure 1; flow chart). No further exclusion criteria were applied. The diagnosis of CS was determined according to the current recommendations of the Acute Cardiovascular Care Association of the European Society of Cardiology [14]. Accordingly, cardiogenic shock was defined by hypotension (systolic blood pressure (SBP) < 90 mmHg) for more than 30 minutes despite adequate filling status or need for vasopressor or inotropic therapy to achieve SBP > 90 mmHg. Additionally, signs for end-organ hypoperfusion must be present such as oliguria with urine output < 30 mL/hour, altered mental status, cold clammy skin, and increased lactate > 2 mmol/L. All-cause mortality at 30 days was documented using the electronic hospital information system and by directly contacting state resident registration offices ("bureau of mortality statistics"). Identification of patients was verified by place of name, surname, date of birth, and registered living address. No patient was lost to follow-up with regard to all-cause mortality at 30 days.

### Measurement of D-dimer levels

D-dimer measurements were performed fully automated using polystyrene particle-enhanced immunoturbidime-

tric measurement from citrate plasma. Platelet-poor plasma was obtained from citrated whole blood for subsequent analysis. Centrifugation was performed according to the manufacturer's recommendations at 2,700 RCF for 15 minutes. The reagent (Innovace D-Dimer, Siemens Healthineers, Erlangen Germany) features a linear measuring range of 0.19 to 4.4 mg/L, expandable to 80.00 mg/L by automated dilution of the analyzer (CS 5100, Sysmex, Kobe, Japan). Specimens showing hemolysis above 200 mg/L are not assessable due to measurement interferences. This is verified automatically prior to the measurement procedure.

**Statistical methods**

Quantitative data is presented as mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution of the data. They were compared using Student's *t*-test for normally distributed data or the Mann-Whitney U test for non-parametric data. Deviations from a Gaussian distribution were tested by the Kolmogorov-Smirnov test. Qualitative data are presented as absolute and relative frequencies and were compared using the chi-squared test or the Fisher's exact test, as appropriate. Box plots for distribution of D-dimer levels were created for the comparisons of survivors and non-survivors. Spearman's rank correlation for nonparametric data was used to test for the association of D-dimer levels with medical and laboratory parameters. C-statistics were applied by calculation of ROC and investigation of the corresponding AUC within the entire cohort to evaluate the prognostic performance of D-dimer levels with regard to the 30-day all-cause mortality.

Kaplan-Meier analyses according to D-dimer levels were performed and univariate hazard ratios (HR) were given together with 95% confidence intervals within the entire study cohort and separated by AMI and non-AMI related CS. The prognostic impact of D-dimer levels was thereafter investigated using multivariate Cox regression models using the "forward selection" option.

Results of all statistical tests were considered significant for $p \leq 0.05$. SPSS (Version 28, IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) and GraphPad Prism (Version 9, GraphPad Software, San Diego, CA, USA) were used for statistics.

## RESULTS

**Study population**

From a total of 273 consecutive patients with CS, D-dimer levels were measured in 136 patients within the first 2 days of ICU treatment. Furthermore, 13 patients with CS related to PE were excluded. Finally, 123 CS patients with a median D-dimer level on admission of 8.440 mg/L were included in the study. Table 1 outlines patients' characteristics stratified by 30-day non-survivors and survivors. Patients had a median age of 68 - 73 years and most patients were males (65% vs. 66%; p = 0.931). Cardiovascular risk factors, such as the rates of arterial hypertension (69% vs. 75%; p = 0.507), diabetes mellitus (40% vs. 35%; p = 0.556), hyperlipidemia (50% vs. 53%; p = 0.764) did not significantly differ among 30-day non-survivors and survivors. In line with this, comparable rates of coronary artery disease (32% vs. 43%; p = 0.711), congestive heart failure (31% vs. 40%; p = 0.292), atrial fibrillation (35% vs. 31%; p = 0.608), and chronic kidney disease (34% vs. 31%; p = 0.732) were observed in both groups.

As illustrated in Table 2, AMI was the most common cause of CS in non-survivors and survivors, whereas the distribution of CS etiology did not differ in non-survivors and survivors (60% vs. 42%; p = 0.345). The presence and extent of coronary artery disease did not significantly differ in both groups (p = 0.136), especially the rates of percutaneous coronary intervention (PCI) (73% vs. 60%; p = 0.179) did not significantly differ among 30-day non-survivors and survivors. On the contrary, 30-day non-survivors presented with higher rates of out-of-hospital cardiac arrest (50% vs. 42%; p = 0.047) and higher norepinephrine doses (median 0.2 µg/kg/minute vs. 0.1 µg/kg/min; p = 0.009). With regard to laboratory data on admission, especially lactate (4.7 mmol/L vs. 2.7 mmol/L; p = 0.001), cardiac troponin I (1.41 vs. 0.23 µg/L; p = 0.001), and D-dimer levels (13.0 vs. 5.2 mg/L; p = 0.011) were higher in the 30-day non-survivor group.

**Correlations with characteristics and laboratory data**

Table 3 displays univariate correlations of D-dimer levels with clinical and laboratory data. D-dimer levels inversely correlated with age (r = -0.238; p = 0.008) and CRP levels (r = -0.256; p = 0.027). In line with this, D-dimer levels correlated with norepinephrine dose (r = 0.445; p = 0.001), lactate (r = 0.277; p = 0.001) and white blood cell (WBC) count (r = 0.206; p = 0.023). On the contrary, no correlations with cardiac biomarkers, such as troponin I (r = 0.074; p = 0.430) and NT-pro BNP levels (r = -0.214; p = 0.149) were demonstrated.

**Prognostic impact of D-dimer levels**

In patients admitted with CS, the overall rate of 30-day all-cause mortality was 55%. D-dimer levels on admission were higher among 30-day non-survivors as compared to 30-day survivors (13.0 vs. 5.2 mg/L; p = 0.011) (Figure 2: box plots). As illustrated in Figure 3, D-dimer level was able to predict all-cause mortality at 30 days in CS patients (AUC = 0.633; 95% CI 0.534 - 0.731; p = 0.012). When stratified by the median D-dimer level on admission, the risk of 30-day all-cause mortality was higher in patients with D-dimer levels > 8.440 mg/L (66% vs. 44%, log rank p = 0.050; HR = 1.594; 95% CI 0.979 - 2.594; p = 0.061; statistical trend) as compared to patients with lower D-dimer levels (Figure 4; left panel). Increased risk of 30-day all-cause mortality was especially seen in patients with in-

**Table 1. Baseline characteristics.**

| | Survivor (n = 55) | | Non-survivor (n = 68) | | p-value |
|---|---|---|---|---|---|
| Age, median; (IQR) | 68 | (60 - 78) | 73 | (61 - 80) | 0.370 |
| Male gender, n (%) | 36 | (65.5) | 44 | (64.7) | 0.931 |
| Body mass index, kg/m$^2$ (median, (IQR)) | 26.00 | (23.98 - 28.35) | 26.50 | (24.40 - 30.10) | 0.309 |
| Vital signs on admission, (median, (IQR)) | | | | | |
| Body temperature (°C) | 36.0 | (35.1 - 36.6) | 35.5 | (34.2 - 36.2) | **0.015** |
| Heart rate (bpm) | 86 | (69 - 104) | 94 | (71 - 117) | 0.188 |
| Systolic blood pressure (mmHg) | 109 | (95 - 131) | 108 | (90 - 127) | 0.478 |
| Respiratory rate (breaths/min) | 20 | (17 - 23) | 20 | (17 - 25) | 0.728 |
| Cardiovascular risk factors, n (%) | | | | | |
| Arterial hypertension | 41 | (74.5) | 47 | (69.1) | 0.507 |
| Diabetes mellitus | 19 | (34.5) | 27 | (39.7) | 0.556 |
| Hyperlipidemia | 29 | (52.7) | 34 | (50.0) | 0.764 |
| Smoking | 21 | (38.2) | 29 | (42.6) | 0.616 |
| Prior medical history, n (%) | | | | | |
| Coronary artery disease | 23 | (42.8) | 22 | (32.4) | 0.711 |
| Congestive heart failure | 22 | (40.0) | 21 | (30.9) | 0.292 |
| Atrial fibrillation | 17 | (30.9) | 24 | (35.3) | 0.608 |
| Chronic kidney disease | 17 | (30.9) | 23 | (33.8) | 0.732 |
| Stroke | 11 | (20.0) | 7 | (10.3) | 0.130 |
| COPD | 9 | (16.4) | 18 | (26.5) | 0.178 |
| Liver cirrhosis | 3 | (5.5) | 3 | (4.4) | 0.790 |
| Medication on admission, n (%) | | | | | |
| ACE-inhibitor | 20 | (36.4) | 21 | (30.9) | 0.521 |
| ARB | 7 | (12.7) | 12 | (17.6) | 0.453 |
| Beta-blocker | 28 | (50.9) | 36 | (52.9) | 0.823 |
| ARNI | 3 | (5.5) | 2 | (2.9) | 0.483 |
| Aldosterone antagonist | 11 | (20.0) | 9 | (13.2) | 0.312 |
| Diuretics | 25 | (45.5) | 33 | (48.5) | 0.734 |
| ASA | 14 | (74.5) | 17 | (25.0) | 0.954 |
| P2Y12-inhibitor | 4 | (7.3) | 4 | (5.9) | 0.756 |
| Statin | 26 | (47.3) | 27 | (39.7) | 0.399 |
| Coronary angiography at index, n (%) | | | | | |
| No evidence of CAD | 6 | (14.3) | 5 | (10.4) | 0.136 |
| 1 - vessel disease | 10 | (23.8) | 5 | (10.4) | |
| 2 - vessel disease | 12 | (28.6) | 11 | (22.9) | |
| 3 - vessel disease | 14 | (33.3) | 27 | (56.3) | |
| CABG | 5 | (11.9) | 3 | (6.3) | 0.347 |
| Chronic total occlusion | 6 | (14.3) | 15 | (31.3) | 0.058 |
| PCI | 25 | (59.5) | 35 | (72.9) | 0.179 |

**ACE - angiotensin-converting-enzyme, ARB - angiotensin receptor blocker, ARNI - angiotensin receptor neprilysin inhibitor, ASA - acetylsalicylic acid, CABG - coronary artery bypass grafting, CAD - coronary artery disease, COPD - chronic obstructive pulmonary disease, IQR - interquartile range, PCI - percutaneous coronary intervention.**
**Level of significance p < 0.05.**

**Table 2. Shock-related data, follow-up data and endpoints.**

| | Survivor (n = 55) | | Non-survivor (n = 68) | | p-value |
|---|---|---|---|---|---|
| **Cause of CS, n (%)** | | | | | |
| **STEMI** | **16** | **(29.9)** | **29** | **(42.6)** | **0.345** |
| **NSTEMI** | **7** | **(12.7)** | **12** | **(17.6)** | |
| **Arrhythmic** | **11** | **(20.0)** | **5** | **(7.4)** | |
| **Pericardial tamponade** | **2** | **(3.6)** | **0** | **(0.0)** | |
| **Takotsubo** | **3** | **(5.5)** | **2** | **(2.9)** | |
| **Ischemic cardiomyopathy** | **2** | **(3.6)** | **5** | **(7.4)** | |
| **Non-ischemic cardiomyopathy** | **1** | **(1.8)** | **3** | **(4.4)** | |
| **Aortic stenosis** | **3** | **(5.5)** | **2** | **(2.9)** | |
| **Mitral regurgitation** | **1** | **(1.8)** | **2** | **(2.9)** | |
| **Tricuspid regurgitation** | **1** | **(1.8)** | **1** | **(1.5)** | |
| **Unknown ADHF** | **8** | **(14.5)** | **7** | **(10.3)** | |
| **Classification of CS, n (%)** | | | | | |
| **Class A** | **0** | **(0.0)** | **0** | **(0.0)** | **0.124** |
| **Class B** | **1** | **(1.8)** | **0** | **(0.0)** | |
| **Class C** | **23** | **(41.8)** | **18** | **(26.5)** | |
| **Class D** | **3** | **(5.5)** | **2** | **(2.9)** | |
| **Class E** | **28** | **(50.9)** | **48** | **(70.6)** | |
| **Transthoracic echocardiography** | | | | | |
| **LVEF > 55%, (n, %)** | **8** | **(14.5)** | **6** | **(8.8)** | |
| **LVEF 54 - 41%, (n, %)** | **5** | **(9.1)** | **5** | **(7.4)** | |
| **LVEF 40 - 30%, (n, %)** | **18** | **(32.7)** | **14** | **(20.6)** | **0.301** |
| **LVEF < 30%, (n, %)** | **22** | **(40.0)** | **39** | **(57.4)** | |
| **LVEF not documented, (n, %)** | **2** | **(3.6)** | **4** | **(5.9)** | |
| **VCI, cm (median, (IQR))** | **1.8** | **(1.5 - 2.2)** | **2.0** | **(1.7 - 2.2)** | **0.747** |
| **TAPSE, mm (median, (IQR))** | **18** | **(12 - 23)** | **14** | **(11 - 17)** | **0.095** |
| **Cardiopulmonary resuscitation** | | | | | |
| **OHCA, n (%)** | **23** | **(41.8)** | **34** | **(50.0)** | **0.047** |
| **IHCA, n (%)** | **5** | **(9.1)** | **14** | **(20.6)** | |
| **Shockable rhythm, n (%)** | **33** | **(60.0)** | **49** | **(72.1)** | **0.158** |
| **Non-shockable rhythm, n (%)** | **22** | **(40.0)** | **19** | **(27.9)** | |
| **ROSC, min (median, IQR)** | **15** | **(8-20)** | **19** | **(12-39)** | **0.035** |
| **Respiratory status** | | | | | |
| **Mechanical ventilation, n (%)** | **38** | **(69.1)** | **46** | **(67.6)** | **0.864** |
| **Duration of mechanical ventilation, days, (mean, (IQR))** | **3** | **(0 - 10)** | **3** | **(1-6)** | **0.656** |
| **$PaO_2/FiO_2$ ratio, (median, (IQR))** | **193** | **(125 - 364)** | **254** | **(142 - 367)** | **0.290** |
| **$PaO_2$, mmHg (median, (IQR))** | **98** | **(74 - 146)** | **110** | **(79 - 171)** | **0.204** |
| **Multiple organ support during ICU** | | | | | |
| **Norepinephrine dose, µg/kg/minute (median, (IQR))** | **0.1** | **(0.0 - 0.2)** | **0.2** | **(0.1 - 0.6)** | **0.009** |
| **Mechanical circulatory assist device, n (%)** | **2** | **(3.6)** | **13** | **(19.1)** | **0.020** |

**Table 2. Shock-related data, follow-up data and endpoints (continued).**

| | Survivor (n = 55) | | Non-survivor (n = 68) | | p-value |
|---|---|---|---|---|---|
| **Baseline laboratory values, (median, (IQR))** | | | | | |
| **pH** | **7.30** | **(7.23 - 7.35)** | **7.27** | **(7.16 - 7.38)** | **0.496** |
| **Lactate (mmol/L)** | **2.7** | **(1.8 - 4.1)** | **4.7** | **(2.5 - 10.2)** | **0.001** |
| **Sodium (mmol/L)** | **138** | **(134 - 140)** | **138** | **(135 - 141)** | **0.666** |
| **Potassium (mmol/L)** | **4.3** | **(3.6 - 4.9)** | **4.2** | **(3.7 - 4.8)** | **0.630** |
| **Creatinine (mg/dL)** | **1.48** | **(1.10 - 2.07)** | **1.49** | **(1.13 - 2.27)** | **0.427** |
| **Hemoglobin (g/dL)** | **12.9** | **(10.6 - 14.6)** | **12.5** | **(11.0 - 14.4)** | **0.943** |
| **WBC ($10^6$/mL)** | **15.03** | **(9.08 - 18.11)** | **15.49** | **(11.60 - 20.06)** | **0.173** |
| **Platelets ($10^6$/mL)** | **222** | **(154 - 283)** | **216** | **(168 - 263)** | **0.671** |
| **PT/INR** | **1.17** | **(1.03 - 1.36)** | **1.18** | **(1.10 - 1.44)** | **0.120** |
| **D-dimer (mg/L)** | **5.22** | **(1.75 - 14.28)** | **12.97** | **(3.27 - 32.00)** | **0.011** |
| **AST (U/L)** | **94** | **(41 - 250)** | **197** | **(53 - 647)** | **0.089** |
| **ALT (U/L)** | **57** | **(28 - 157)** | **86** | **(34 - 289)** | **0.215** |
| **Bilirubin (mg/dL)** | **0.61** | **(0.37 - 1.11)** | **0.76** | **(0.48 - 1.58)** | **0.112** |
| **Troponin I (µg/L)** | **0.229** | **(0.086 - 0.788)** | **1.413** | **(0.425 - 12.430)** | **0.001** |
| **NT-pro BNP (pg/mL)** | **5,702** | **(519 - 15,163)** | **3438** | **(979 - 22,115)** | **0.966** |
| **Procalcitonin (ng/mL)** | **0.35** | **(0.16 - 0.88)** | **0.96** | **(0.23 - 3.07)** | **0.285** |
| **CRP (mg/L)** | **9** | **(4 - 42)** | **12** | **(4 - 35)** | **0.664** |
| **Primary endpoint** | | | | | |
| **All-cause mortality at 30 days, n (%)** | **0** | **(0.0)** | **68** | **(100.0)** | **-** |
| **Follow up data, n (%)** | | | | | |
| **ICU time, days (median, (IQR))** | **8** | **(4 - 14)** | **4** | **(2 - 6)** | **0.001** |
| **Death ICU, n (%)** | **3** | **(5.5)** | **64** | **(94.1)** | **0.001** |

**ADHF - acute decompensated heart failure, ALT - alanine aminotransferase, AST - aspartate aminotransferase, CRP - C-reactive Protein, ICU - intensive care unit, IHCA - in-hospital cardiac arrest, IQR - interquartile range, NSTEMI - non-ST-segment myocardial infarction, NT-pro BNP - aminoterminal pro-B-type natriuretic peptide, OHCA - out-of-hospital cardiac arrest, PT/INR - international normalized ratio, ROSC - return of spontaneous circulation, STEMI - ST-segment myocardial infarction, TAPSE tricuspid annular plane systolic excursion, VCI - vena cava inferior, WBC - white blood cells.**
**Level of significance p < 0.05. Underlined type indicates statistical significance.**

creased D-dimer levels admitted with non-AMI related CS (65% vs. 30%, log rank p = 0.010; HR = 2.643; 95% CI 1.206 - 5.791; p = 0.015), whereas D-dimer levels did not predict the risk of 30-day all-cause mortality in AMI-related CS patients (67% vs. 61%, log rank p = 0.932) (Figure 4; middle and right panel).

### Multivariate risk prediction model

Even after multivariate adjustment, D-dimer level was still associated with increased risk of the primary endpoint (HR = 1.024; 95% CI 1.004 - 1.045; p = 0.030) (Table 4). Furthermore, SBP (HR = 0.989; p = 0.012) and lactate (HR = 1.109; p = 0.001) were associated with the risk of all-cause mortality within the multivariate risk prediction model.

## DISCUSSION

The present study sought to investigate the prognostic value of D-dimer levels in consecutive CS patients admitted to an internistic ICU. The data suggests, D-dimer levels on admission were significantly higher among 30-day non-survivors as compared to survivors. In line, patients with higher D-dimer levels were associated with increased risk of 30-day all-cause mortality, which was specifically observed in patients with CS not related to AMI. The prognostic value of D-dimer levels was still observed after multivariate adjustment.

Data demonstrating the adverse prognostic impact of high D-dimer levels is typically derived from patients with coronary artery disease, AMI or heart failure, whereas CS patients were usually beyond the score of

**Table 3. Correlations of D-dimer concentrations with clinical and laboratory parameters in all patients on day 1.**

| | D-dimer | |
|---|---|---|
| | r | p-value |
| Age | -0.238 | 0.008 |
| Body mass index (kg/m$^2$) | 0.065 | 0.483 |
| $PaO_2/FiO_2$ ratio | -0.008 | 0.932 |
| Norepinephrine (µg/kg/minute) | 0.445 | 0.001 |
| Lactate (mmol/L) | 0.277 | 0.002 |
| Creatinine (mg/dL) | 0.002 | 0.986 |
| Hemoglobin (g/dL) | 0.161 | 0.076 |
| WBC ($10^6$/mL) | 0.206 | 0.023 |
| Platelet count ($10^6$/mL) | -0.115 | 0.208 |
| INR | 0.033 | 0.719 |
| Bilirubin (mg/dL) | -0.017 | 0.892 |
| Troponin I (µg/L) | 0.074 | 0.430 |
| NT-pro BNP (pg/mL) | -0.214 | 0.149 |
| Procalcitonin (ng/mL) | 0.297 | 0.079 |
| CRP (mg/L) | -0.256 | 0.005 |

**CRP - C-reactive protein, INR - international normalized ratio, NT-pro BNP - aminoterminal pro-B-type natriuretic peptide, WBC - white blood cells.**
**Level of significance p < 0.05. Underlined type indicates statistical significance.**

**Table 4. Uni- and multivariate Cox regression analyses with regard to 30-day all-cause mortality within the entire study cohort.**

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Age | 1.004 | 0.987 - 1.021 | 0.654 | 1.016 | 0.998 - 1.034 | 0.085 |
| Heart rate (bpm) | 1.007 | 0.999 - 1.015 | 0.074 | 1.002 | 0.994 - 1.010 | 0.679 |
| Systolic blood pressure (mmHg) | 0.992 | 0.983 - 1.001 | 0.067 | 0.989 | 0.981 - 0.998 | 0.012 |
| Lactate (mmol/L) | 1.116 | 1.074 - 1.161 | 0.001 | 1.109 | 1.056 - 1.165 | 0.001 |
| Creatinine (mg/dL) | 1.049 | 0.907 - 1.214 | 0.518 | 1.030 | 0.865 - 1.227 | 0.740 |
| Troponin I (µg/L) | 1.002 | 1.000 - 1.003 | 0.012 | 1.001 | 1.000 - 1.003 | 0.072 |
| D-dimer (mg/L) | 1.026 | 1.009 - 1.043 | 0.002 | 1.024 | 1.004 - 1.045 | 0.020 |

**Level of significance p < 0.05.**

prior studies. For instance, Koch et al. demonstrated D-dimer levels were associated with reliable predictive value to discriminate patients with ST-segment elevation myocardial infarction (STEMI) from patients with non-coronary chest pain including 3,557 patients with suspected acute coronary syndrome. In line, increased D-dimer levels were associated with higher rates of recurrent AMI and all-cause mortality [15]. Furthermore, higher D-dimer levels were associated with increased risk of in-hospital mortality, as well as long-term mortality at 6 months including 453 STEMI patients treated with PCI [16].

Within the present study, AMI was the most common cause of CS. However, within the present study, D-dimer levels were not associated with prognosis in the presence of AMI-related CS, whereas D-dimer levels were able to discriminate 30-day all-cause mortality in patients with CS not related to AMI. Although most studies suggested increased D-dimer levels were associated with unfavorable outcomes following AMI, those

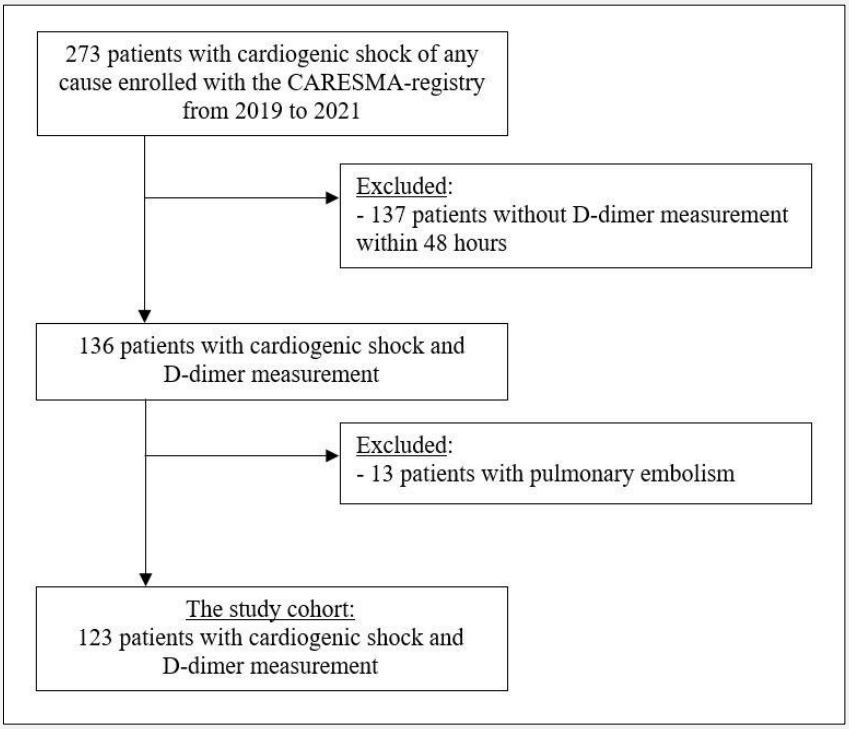


**Figure 1. Study flow chart.**

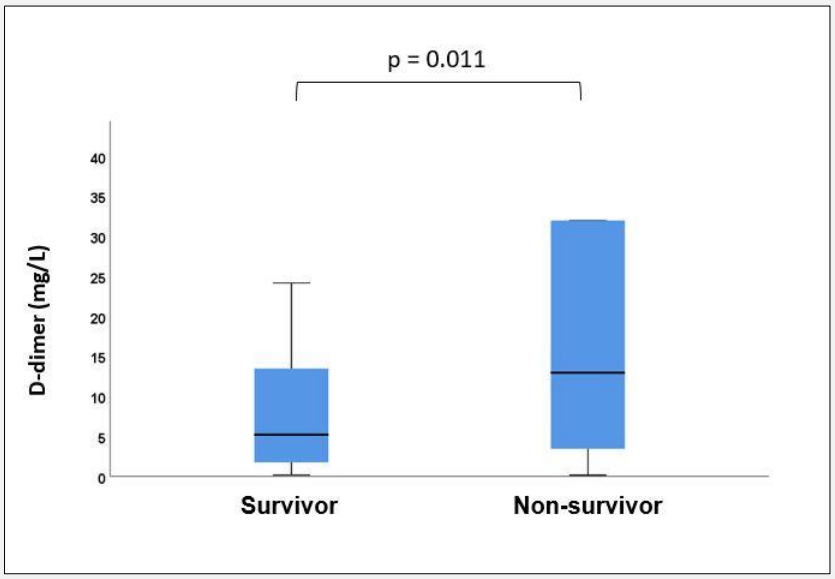


**Figure 2. Box plots demonstrating the distribution of D-dimer levels among 30-day survivors and non-survivors with CS on admission. The data is presented as the median with interquartile ranges (boxes) and 5 - 95% percentiles (whiskers).**

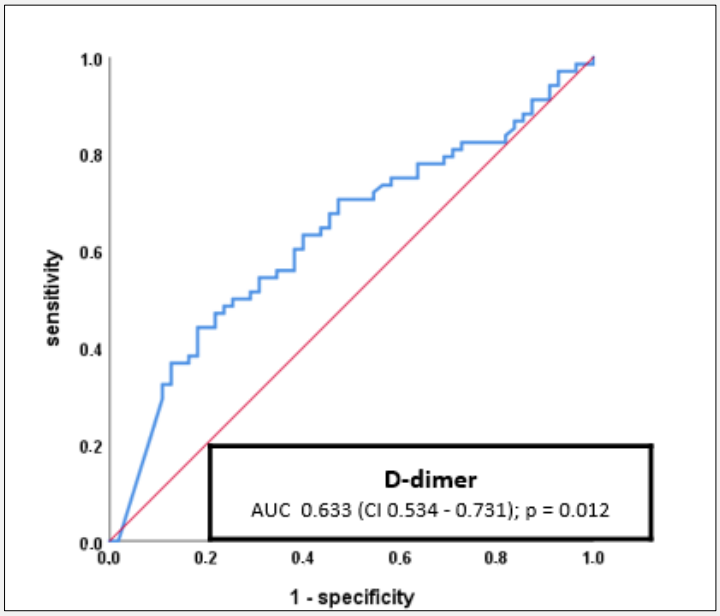


**Figure 3. Receiver operating characteristic curve (ROC) analyses investigating the prognostic performance of D-dimer levels with regard to 30-day all-cause mortality.**

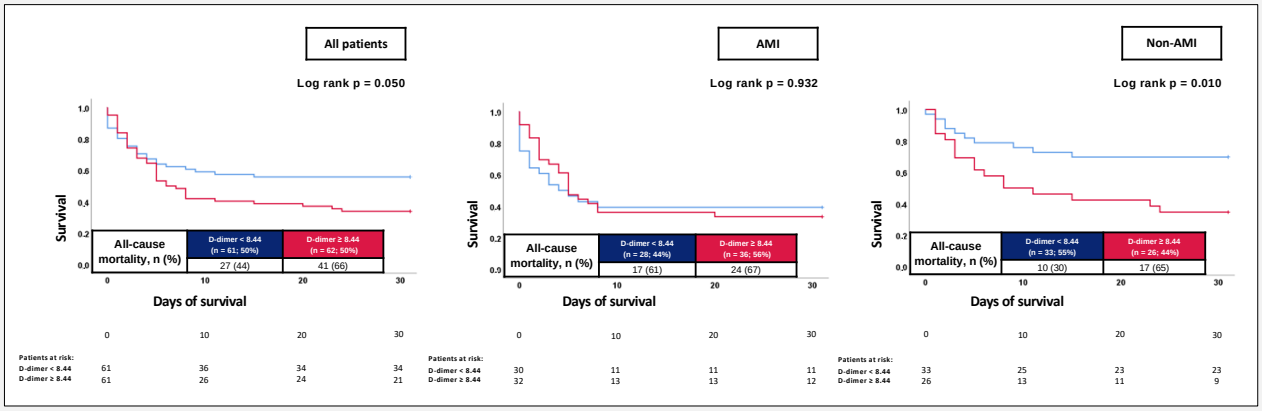


**Figure 4. Prognostic impact of D-dimer levels on admission on the risk of all-cause mortality at 30 days within the entire study cohort (left panel), as well as stratified by patients with AMI-related CS (middle panel) and non-AMI related CS (right panel).**

studies did not investigate the role of D-dimer levels in subgroups of CS patients [17]. Even in AMI patients, studies are characterized by heterogenous findings. For instance, higher D-dimer levels were not associated with prognosis among 234 patients with NSTEMI [18]. Thus, patients' characteristics of those with AMI enrolled in registries and patients with AMI-related CS differ significantly. Especially the extent of coronary artery

disease was higher among patients who developed CS, alongside with higher rates of chronic total occlusions (CTO), whereas LVEF was shown to be significantly lower in CS patients [19], which decreases the comparability of AMI patients with and without CS. Accordingly, in paucity of the up to 10 times higher mortality rates in AMI-related CS compared to AMI patients without CS on admission, the present study provides further insights. Therefore, comprehensive analyses are needed to identify the optimal biomarker in AMI-related CS, since D-dimer level assessments were beyond the scope of the recently published CULPRIT-SHOCK trial [20].

From a pathophysiological aspect, D-dimer is generated during fibrinolysis as a break-down product of cross-linked fibrin. Thus, D-dimer was shown to correlate with coagulation, thrombus burden, and intravascular fibrinolysis [21,22]. Alongside with these findings, D-dimer levels were shown to correlate with infarction size, which was demonstrated in 208 STEMI patients undergoing cardiac magnetic resonance (CMR) imaging [23] and were demonstrated to predict no-reflow following PCI for STEMI in 822 patients with concomitant type 2 diabetes mellitus [24]. Furthermore, D-dimer levels were shown to increase in patients with severe arteriosclerosis and to correlate with the amount of fibrin [25]. However, within the present registry, most patients presented with multi-vessel disease which was observed both in survivors and non-survivors, which may be in line with overall high median D-dimer levels within the present study. Of note, increased D-dimer levels may not only correlate with thrombus burden and resulting infarction size but also with shock-related blood stasis in the setting of decreased cardiac output related to the so-called “Virchow triad”, including blood stasis, hypercoagulable state and endothelial dysfunction, alongside with a higher prevalence of thromboembolic events as compared to patients without heart failure [26]. In this setting, higher D-dimer levels may be in line with more severe stages of CS, alongside increased lactate levels, creatinine, and NT-pro BNP, which were recently identified as prognostic biomarkers in CS patients [20]. However, even after multivariate adjustment, D-dimer levels were still associated with the risk of 30-day all-cause mortality in CS patients, suggesting D-dimer represents an independent predictor of prognosis following CS.

The prognostic role of D-dimer levels was also investigated within various studies including patients with acute or chronic heart failure. D-dimer levels were associated with the risk of cardiovascular mortality among 174 consecutive patients with systolic heart failure [27]. Furthermore, D-dimer levels were associated with good diagnostic accuracy for ADHF in 162 patients with ADHF compared to 253 matched controls, whereas no correlations of D-dimer levels with echocardiographic parameters were found [28]. Moreover, higher D-dimer levels were associated with an increased risk of ischemic stroke in 721 patients with ADHF with mean LVEF of 38% [29]. Within the present study, ADHF-related CS was the most common cause of CS apart from AMI. Thus, it was demonstrated for the first time, that D-dimer levels were higher in patients with non-survivors with non-AMI related CS and D-dimer levels were able to discriminate the risk of 30-day all-cause mortality in patients admitted with CS not related to AMI.

However, the setting of CS is associated with various complications, that may further contribute to higher and specifically increasing D-dimer levels during the course of ICU treatment. For instance, D-dimer levels were frequently shown to be increased in patients with concomitant infection or sepsis and may indicate disseminated intravascular coagulation, which is associated with impaired prognosis [30]. Although the D-dimer increase in the setting of CS may be multifactorial, this is - to the best knowledge of the authors - the first study to investigate the association with D-dimer levels and all-cause mortality in patients with CS of any cause.

In conclusion, the present study suggests D-dimer levels were able to discriminate 30-day all-cause mortality in CS patients. Increased risk of 30-day all-cause mortality in CS patients with higher D-dimer levels was consistent after multivariate adjustment.

**Study limitations**

This study has several limitations. Due to the single-center and observational study design, results may be influenced by measured and unmeasured confounding factors. D-dimer was only infrequently measured during course of ICU hospitalization, therefore no analysis focusing on the prognostic value of D-dimer increase or decrease was performed. For the present study, no age-normalized D-dimer assessment was used, although it was shown that D-dimer levels are affected by age. However, multivariate Cox regression models were adjusted for age, suggesting an independent association of D-dimer levels with the risk of 30-day all-cause mortality. Finally, no information on long-term mortality was available for the present study.

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**Declaration of Interest:**

Thomas Bertsch performed an evaluation study for a D-dimer assay from Roche Diagnostics. The other authors declare that they do not have any conflict of interest.

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