Regional differences in presentation characteristics, use of treatments and outcome of patients with cardiogenic shock: Results from multicenter, international registry

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Background. Concurrent evidence about cardiogenic shock (CS) characteristics, treatment and outcome does not represent a global spectrum of patients and is therefore limited. The aim of this study was to investigate these regional differences.

Methods. To investigate regional differences in presentation characteristics, treatments and outcomes of patients treated with all types of cardiogenic shock (CS) in a single calendar year on a multi-national level. Consecutive patients from 19 tertiary care hospitals in 13 countries with CS who were treated between January 1, 2018 and December 31, 2018 were enrolled in this study.

Results. In total, 699 cardiogenic shock patients were included in this study. Of these patients, 440 patients (63%) were treated in European hospitals and 259 (37%) were treated in Non-European hospitals. Female patients ($P<0.01$) and patients with a previous myocardial infarction ($P=0.02$) were more likely to present at Non-European hospitals; whereas older patients ($P=0.01$) and patients with cardiogenic shock due to acute heart failure ($P<0.01$) were more likely to present at European hospitals. Vasopressor use was more likely in Non-European hospitals ($P=0.04$), whereas use of mechanical circulatory support (MCS) was more likely in European hospitals ($P<0.01$). Despite adjustment for relevant confounders, 30-day in-hospital mortality risk was comparably high in CS patients treated in European vs. Non-European hospitals (hazard ratio 1.08, 95% CI 0.84-1.39, $P=0.56$).

Conclusion. Despite marked heterogeneity in characteristics and treatment of CS patients, including fewer use of MCS but more frequent use of vasopressors in Non-European hospitals, 30-day in-hospital mortality did not differ between regions.

Key words: cardiogenic shock, regional differences, mechanical circulatory support, acute heart failure, AMICS

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INTRODUCTION

Despite advances in early revascularization and use of mechanical circulatory support (MCS), cardiogenic shock (CS) is still associated with extremely high mortality. Although there is no uniform definition, CS is a low cardiac output state, primarily due to a cardiac dysfunction, resulting in life-threatening end-organ hypoperfusion and hypoxia¹.

Concurrent evidence about CS characteristics, management and outcome might be hampered by several confounders, as it does not represent a global spectrum of patients. First, patient populations have always been predominantly investigated on a national level, and studies based on multi-national cohorts, especially including non-developed countries, are scarce²⁻⁴. Second, most of the data from registries, observational studies and prospective trials have been derived from high-income countries that possess high quality health care, with more advanced interventional treatment programs, including MCS (ref.⁵⁻⁸). And third, the vast majority of studies included solely acute coronary syndrome (ACS) related cases, while not including other etiologies, such as myocardial stunning following cardiac arrest or acute heart failure exacerbation⁹⁻¹¹. This might have a relevant impact, as recent studies indicated that the proportion of CS cases caused by ACS is declining, and that the majority of cases is caused by non-ischemic events^{4,12}.

Hypothesis and purpose

Regional differences in diagnosis, as well as regional differences per se, could influence management and

outcome in CS. The aim of this study was to investigate regional differences in presentation characteristics, treatments and outcomes of patients treated with all types of CS in a single calendar year on a multi-national level.

METHODS

This project was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committees. Need for informed consent was waived as this was a retrospective analysis of anonymized data.

Study population

From 19 tertiary care hospitals in 13 countries, consecutive patients with CS who were treated between January 1, 2018 and December 31, 2018 were enrolled in a dedicated database. CS, the only inclusion criterion, was defined at the discretion of the local investigator. The only exclusion criterion of this study was age below 18 years. For all included patients, baseline characteristics and in-hospital follow-up were available.

Patients were then stratified as being treated in European countries (Belgium, Czech Republic, Greece, Italy, Portugal, Serbia, Slovakia and Germany) vs. non-European countries (Egypt, Kuwait, Mexico, Peru, Russia and Uzbekistan).

Statistical analysis

Continuous variables are shown as mean ($\pm$ standard deviation) and compared using t-test; binary variables are

Fig. 1. Differences in presentation characteristics and use of treatments of cardiogenic shock patients treated in European vs. Non-European countries.
eCPR: extracorporeal cardiopulmonary resuscitation.

shown as counts (frequencies) and compared using the Chi² test.

Missing data were handled by chained equation multiple imputation (10 imputed data sets; R package mice). Variables used for the imputation of missing data are shown in Table 1.

To assess differences in presentation characteristics and use of treatments between patients with cardiogenic shock treated at European vs. non-European countries, a logistic regression model with location of treatment as the dependent variable and selected presentation characteristics/treatments as independent variables was fitted (Fig. 1).

To assess differences in outcome between patients with CS treated in European vs. non-European countries, the primary endpoint of 30-day in-hospital mortality was analyzed, whereas patients were censored upon discharge from hospital. Survival probabilities were estimated using the Kaplan-Meier method. To assess the association of region of treatment with the primary endpoint, a Cox regression model was fitted, (a) unadjusted and (b) adjusted for age, sex, cause of cardiogenic shock, prior cardiac arrest, extracorporeal cardiopulmonary resuscitation (eCPR), baseline lactate and baseline pH.

A *P*-value of <0.05 was considered statistically significant. All analyses were performed with R statistical software version 3.6.0.

Table 1. Baseline characteristics of the study cohort.

Variable	Overall cohort (n=699)	European (n=440, 63%)	Missing (%)	Non-European (n=259, 37%)	Missing (%)	<i>P</i>
Age, years	63.90 (±14.77)	65.01 (±14.01)	0	62.01 (±15.82)	0	<0.01
Age, ≥65 years	369 (52.8)	243 (55.2)		126 (48.6)		0.11
Female sex	235 (33.6)	133 (30.2)	0	102 (39.4)	0	0.02
BMI, kg/m ²	27.39 (±4.96)	27.21 (±4.76)	11.6	27.68 (±5.25)	5.8	0.25
Obesity (BMI >30 kg/m ²)	451 (71.1)	287 (73.8)		164 (66.9)		0.08
Diabetes mellitus	247 (35.6)	136 (31.3)	1.4	111 (42.9)	0	<0.01
Arterial hypertension	449 (64.8)	284 (65.4)	1.4	165 (63.7)	0	0.70
Dyslipidemia	268 (38.7)	153 (35.3)	1.4	115 (44.4)	0	0.02
Active smoker	178 (25.7)	101 (23.3)	1.4	77 (29.7)	0	0.07
Previous myocardial infarction	189 (27.3)	103 (23.7)	1.4	86 (33.2)	0	<0.01
Chronic renal failure	168 (24.2)	94 (21.7)	1.4	74 (28.4)	0	0.03
Previous stroke	72 (10.4)	39 (9.0)	1.4	33 (12.7)	0	0.15
Systolic blood pressure, mmHg	83.52 (±23.07)	86.34 (±23.74)	17.3	79.51 (±21.50)	0.8	<0.01
Heart rate, beats per minute	94.34 (±30.48)	96.14 (±31.85)	20.9	91.89 (±28.39)	1.2	0.09
Lactate, mmol/L	5.89 (±4.99)	6.07 (±5.38)	18.2	5.55 (±4.15)	24.7	0.23
Lactate, <2.9 mmol/L	182 (32.8)	125 (34.7)		57 (29.2)		
Lactate, 2.9-6.3 mmol/L	186 (33.5)	117 (32.5)		69 (35.4)		0.42
Lactate, >6.3 mmol/L	187 (33.7)	118 (32.8)		69 (35.4)		
pH	7.29 (±0.15)	7.29 (±0.17)	11.6	7.29 (±0.12)	15.4	0.83
pH, <7.25	195 (32.1)	124 (31.9)		71 (32.4)		
pH, 7.25-7.37	220 (36.2)	132 (33.9)		88 (40.2)		0.17
pH, >7.37	193 (31.7)	133 (34.2)		60 (27.4)		
Cause of cardiogenic shock			0.7		0.4	
Acute myocardial infarction	422 (60.7)	250 (57.2)		172 (66.7)		
Acute heart failure	164 (23.6)	118 (27.0)		46 (17.8)		0.02
Other	109 (15.7)	69 (15.8)		40 (15.5)		
Prior cardiac arrest	314 (44.9)	206 (46.8)	0	108 (41.7)	0	0.22
Duration of cardiac arrest, min	19.81 (±25.41)	21.75 (±31.04)	10.5	16.86 (±12.39)	10.4	0.10
eCPR	34 (5.5)	24 (0.3)	13.2	10 (4.2)	7.3	0.34
Mechanical circulatory support	210 (30.0)	147 (33.4)	0	63 (24.3)	0	0.01
IABP	161 (23.0)	98 (22.3)		63 (24.3)		0.60
Impella	71 (10.2)	68 (15.5)		3 (1.2)		<0.01
ECMO	80 (11.4)	65 (14.8)		15 (5.8)		<0.01
Vasopressor use	564 (81.9)	346 (78.8)	0.2	218 (87.2)	3.5	<0.01
Inotrope use	531 (77.3)	336 (76.5)	0.2	195 (78.6)	4.2	0.59
Calcium sensitizer use	114 (16.4)	69 (15.8)	0.5	45 (17.4)	0.4	0.64
Mechanical ventilation	479 (68.7)	309 (70.4)	0.2	170 (65.9)	0.4	0.25

Continuous variables are shown as mean (±standard deviation) and compared using t-test; binary variables are shown as counts (frequencies) and compared using the Chi² test. BMI – body mass index; eCPR- extracorporeal cardiopulmonary resuscitation; ECMO – extracorporeal membrane oxygenation; IABP – intra-aortic balloon pump

Fig. 2. Outcome in cardiogenic shock patients treated in European vs. Non-European countries.
HR: hazard ratio; CI: confidence interval.

RESULTS

In total, 699 CS patients were included in this study. Of these patients, 440 patients (63%) were treated in European hospitals and 259 (37%) were treated in Non-European hospitals. The mean age of the overall study cohort was 63.90 (± 14.77) years and 235 patients (33.6%) were females. Within the overall cohort, 422 patients (60.7%) presented with cardiogenic shock due to ACS, 164 patients (23.6%) presented with CS due to acute heart failure and 314 patients (44.9%) had a prior cardiac arrest. At baseline, mean lactate was 5.89 ± 4.99 mmol/l and mean pH was 7.29 ± 0.15 . Detailed baseline characteristics per region are shown in Table 1, and baseline characteristics per country are shown in Table 2

Presentation characteristics and use of treatments

Baseline characteristics in Table 1 are unadjusted. Therefore, we performed multivariable adjusted logistic regression to identify if dedicated presentation characteristics or use of treatments was significantly associated with care at a European vs. a Non-European hospital (Fig. 1). In this analysis, female patients and patients with a previous myocardial infarction were more likely to be treated at Non-European hospitals; whereas older patients, patients with arterial hypertension and patients with CS due to acute heart failure were more likely to be treated at European hospitals. Regarding treatments, vasopressor use was more likely in Non-European hospitals whereas use of MCS was more likely in European hospitals.

Outcome

During a median follow-up of 10 (interquartile range 4-30) days (9 days in European vs. 12 days in Non-European patients, $P < 0.01$), 303 deaths (43.3%) occurred

within 30 days after hospital admission in the overall cohort, corresponding to an unadjusted survival probability of 45% [95% confidence interval (CI) 40.2-50.2%]. Unadjusted survival probabilities in patients treated at European vs. Non-European hospitals were 44.8% (95% CI 39.3-50.9%) vs. 45.3% (95% CI 35.8-57.3%).

In the unadjusted Cox regression analysis, there was no significant difference in 30-day mortality risk between CS patients treated at European vs. Non-European (hazard ratio 0.95, 95% CI 0.75-1.21, $P = 0.68$). This did not change after adjustment for relevant confounders (hazard ratio 1.08, 95% CI 0.84-1.39, $P = 0.56$) (Fig. 2).

DISCUSSION

The principal findings from this international registry on CS can be summarized as follows: 1) Despite marked heterogeneity in characteristics and treatment of CS patients, 30-day all-cause mortality did not differ between European and Non-European patients. 2) Patients with CS treated in non-European hospitals were younger, more likely to be female and to have had a prior myocardial infarction, but less likely to have CS due to acute decompensated heart failure. 3) Although, no differences in initial shock severity was observed (pH, lactate), non-European patients were more likely to be treated with vasopressors, but less likely to be treated with MCS. These findings are of major importance, as they reveal significant regional differences in treatment of CS, although shock severity and mortality risk were comparable between patients treated at European and Non-European hospitals.

Current evidence about CS contains predominantly data derived from single nation registries and studies conducted in developed countries (Germany, USA, France, Switzerland, Japan, etc.) (ref.²⁻¹²). Notably, as Vallabhajosyula et al. reported in their nationally representative database from the United States, there seems to be a significant geographic heterogeneity in the epidemiology, management and outcomes of CS across one country¹¹. Our study confirmed this heterogeneity in terms of causes of CS, clinical presentation, and treatment on a multinational level.

Furthermore, CS has a large phenotypic variability, as result of the diverse etiologies, pathogenetic mechanisms, and stages of severity. In past registries, the significant majority of CS cases in the cardiac intensive care unit was caused by ACS (ref.⁹⁻¹¹). However, the contribution of ACS has declined over the past 2 decades³ in parallel with an increase of CS due to other etiologies^{4,12}.

The current study spans 19 centers in 13 different countries (6 of them are outside Europe - Africa, Asia and South America) and therefore allows us to report disparities in CS patients across the world.

Average age of patients presenting with CS in Western countries is 67-72 years^{3,9,11}, whereas more than a decade lower age at presentation was documented in an Indian cohort with STEMI related CS (ref.¹³). We observed a similar trend in our cohort, where younger patients were

Table 2. Baseline characteristics of the study cohort per country.

	Belgium (n=23)	Czech Republic (n=46)	Egypt (n=67)	Germany (n=47)	Greece (n=22)	Italy (n=119)	Kuwait (n=9)	Mexico (n=66)	Peru (n=29)	Portugal (n=23)	Russia (n=73)	Serbia (n=100)	Slovakia (n=60)	Uzbekistan (n=15)
Age, years	65.61 (±15.32)	57.80 (±15.44)	59.37 (±11.14)	62.19 (±14.11)	49.05 (±16.79)	66.52 (±12.54)	59.00 (±14.91)	54.53 (±22.63)	69.69 (±11.47)	71.35 (±13.36)	67.26 (±10.53)	68.39 (±12.07)	67.33 (±11.10)	68.13 (±8.93)
Age, categorized														
<65 years	8 (34.8)	32 (69.6)	45 (67.2)	25 (53.2)	17 (77.3)	49 (41.2)	5 (55.6)	40 (60.6)	7 (24.1)	8 (34.8)	31 (42.5)	36 (36.0)	22 (36.7)	5 (33.3)
≥65 years	15 (65.2)	14 (30.4)	22 (32.8)	22 (46.8)	5 (22.7)	70 (58.8)	4 (44.4)	26 (39.4)	22 (75.9)	15 (65.2)	42 (57.5)	64 (64.0)	38 (63.3)	10 (66.7)
Female sex	9 (39.1)	12 (26.1)	24 (35.8)	9 (19.1)	8 (36.4)	28 (23.5)	3 (33.3)	32 (48.5)	3 (10.3)	9 (39.1)	34 (46.6)	40 (40.0)	18 (30.0)	6 (40.0)
BMI, kg/m ²	27.11 (±4.76)	27.85 (±5.26)	31.08 (±4.92)	27.08 (±4.83)	26.15 (±7.10)	26.07 (±3.97)	26.89 (±2.96)	24.36 (±5.75)	27.69 (±3.48)	26.30 (±5.42)	27.79 (±4.13)	27.01 (±3.51)	29.93 (±5.37)	26.47 (±2.90)
Obesity (BMI >30 kg/m ²)	11 (47.8)	31 (68.9)	30 (44.8)	18 (64.3)	13 (65.0)	84 (84.0)	7 (77.8)	55 (85.9)	20 (69.0)	16 (69.6)	40 (65.6)	80 (80.0)	34 (60.7)	12 (80.0)
Diabetes mellitus	8 (34.8)	17 (37.8)	42 (62.7)	11 (26.2)	7 (31.8)	33 (27.7)	5 (55.6)	19 (28.8)	7 (24.1)	7 (30.4)	28 (38.4)	37 (37.0)	16 (26.7)	10 (66.7)
Arterial hypertension	15 (65.2)	30 (66.7)	43 (64.2)	23 (54.8)	8 (36.4)	69 (58.0)	8 (88.9)	19 (28.8)	15 (51.7)	17 (73.9)	67 (91.8)	78 (78.0)	44 (73.3)	13 (86.7)
Dyslipidemia	10 (43.5)	18 (40.0)	47 (70.1)	15 (35.7)	5 (22.7)	46 (38.7)	5 (55.6)	9 (13.6)	8 (27.6)	10 (43.5)	33 (45.2)	33 (33.0)	16 (26.7)	13 (86.7)
Active smoker	5 (21.7)	12 (26.7)	36 (53.7)	11 (26.2)	15 (68.2)	21 (17.6)	7 (77.8)	12 (18.2)	5 (17.2)	5 (21.7)	11 (15.1)	22 (22.0)	10 (16.7)	6 (40.0)
Previous myocardial infarction	6 (26.1)	13 (28.9)	25 (37.3)	8 (19.0)	8 (36.4)	30 (25.2)	4 (44.4)	15 (22.7)	7 (24.1)	4 (17.4)	24 (32.9)	24 (24.0)	10 (16.7)	11 (73.3)
Chronic renal failure	5 (21.7)	1 (2.2)	15 (22.4)	8 (19.0)	5 (22.7)	33 (27.7)	5 (55.6)	3 (4.5)	1 (3.4)	4 (17.4)	43 (58.9)	29 (29.0)	6 (10.0)	7 (46.7)
Previous stroke	2 (8.7)	7 (15.2)	10 (14.9)	2 (4.8)	0 (0.0)	7 (5.9)	4 (44.4)	4 (6.1)	3 (10.3)	1 (4.3)	11 (15.1)	12 (12.1)	8 (13.3)	1 (6.7)
Systolic blood pressure, mmHg	91.12 (±14.82)	105.00 (±27.06)	69.75 (±13.94)	91.17 (±25.22)	87.48 (±16.49)	81.53 (±10.71)	78.89 (±4.86)	84.55 (±10.23)	79.97 (±8.24)	86.64 (±14.60)	83.94 (±34.74)	74.62 (±15.45)	94.31 (±37.63)	79.47 (±10.66)
Heart rate, beats per minute	92.27 (±30.36)	93.23 (±27.81)	98.17 (±27.45)	107.37 (±30.68)	119.52 (±18.22)	101.30 (±32.20)	110.44 (±5.08)	89.26 (±24.23)	108.69 (±22.79)	81.82 (±39.34)	77.40 (±30.01)	91.88 (±29.32)	89.41 (±33.71)	101.60 (±25.98)
Lactate, mmol/L	4.81 (±4.08)	5.05 (±5.54)	6.74 (±3.25)	8.87 (±7.06)	2.51 (±1.55)	4.84 (±4.06)	5.66 (±1.41)	5.14 (±4.93)	5.88 (±4.17)	4.81 (±3.03)	6.14 (±3.70)	6.47 (±4.00)	13.94 (±9.64)	0.37 (±0.90)
Lactate, categorized														
<2.9 mmol/L	12 (54.5)	23 (54.8)	1 (2.1)	9 (20.0)	16 (72.7)	42 (45.2)	0 (0.0)	26 (45.6)	9 (31.0)	4 (19.0)	8 (20.0)	19 (19.2)	0 (0.0)	13 (100.0)
>6.3 mmol/L	7 (31.8)	10 (23.8)	22 (46.8)	22 (48.9)	0 (0.0)	25 (26.9)	3 (33.3)	14 (24.6)	13 (44.8)	2 (9.5)	17 (42.5)	40 (40.4)	12 (75.0)	0 (0.0)
2.9-6.3 mmol/L	3 (13.6)	9 (21.4)	24 (51.1)	14 (31.1)	6 (27.3)	26 (28.0)	6 (66.7)	17 (29.8)	7 (24.1)	15 (71.4)	15 (37.5)	40 (40.4)	4 (25.0)	0 (0.0)
pH	7.31 (±0.10)	7.36 (±0.18)	7.28 (±0.07)	7.22 (±0.22)	7.33 (±0.10)	7.34 (±0.13)	7.27 (±0.02)	7.34 (±0.15)	7.25 (±0.13)	7.36 (±0.08)	7.26 (±0.13)	7.26 (±0.15)	7.22 (±0.22)	7.33 (±0.13)
pH, categorized														
<7.25	5 (22.7)	8 (19.0)	17 (26.6)	19 (43.2)	4 (18.2)	22 (22.0)	1 (11.1)	19 (31.1)	12 (41.4)	2 (10.0)	18 (43.9)	44 (44.4)	20 (50.0)	4 (26.7)
>7.37	6 (27.3)	28 (66.7)	7 (10.9)	10 (22.7)	8 (36.4)	43 (43.0)	0 (0.0)	31 (50.8)	4 (13.8)	7 (35.0)	9 (22.0)	21 (21.2)	10 (25.0)	9 (60.0)
7.25-7.37	11 (50.0)	6 (14.3)	40 (62.5)	15 (34.1)	10 (45.5)	35 (35.0)	8 (88.9)	11 (18.0)	13 (44.8)	11 (55.0)	14 (34.1)	34 (34.3)	10 (25.0)	2 (13.3)
Cause of cardiogenic shock														
Acute myocardial infarction	15 (71.4)	15 (32.6)	46 (68.7)	22 (46.8)	8 (36.4)	67 (56.3)	6 (66.7)	15 (23.1)	22 (75.9)	12 (54.5)	70 (95.9)	81 (81.0)	30 (50.0)	13 (86.7)
Acute heart failure	3 (14.3)	22 (47.8)	17 (25.4)	15 (31.9)	11 (50.0)	19 (16.0)	3 (33.3)	21 (32.3)	1 (3.4)	4 (18.2)	2 (2.7)	14 (14.0)	30 (50.0)	2 (13.3)
Other	3 (14.3)	9 (19.6)	4 (6.0)	10 (21.3)	3 (13.6)	33 (27.7)	0 (0.0)	29 (44.6)	6 (20.7)	6 (27.3)	1 (1.4)	5 (5.0)	0 (0.0)	0 (0.0)
Prior cardiac arrest	13 (56.5)	13 (28.3)	18 (26.9)	28 (59.6)	5 (22.7)	43 (36.1)	5 (55.6)	30 (45.5)	9 (31.0)	2 (8.7)	31 (42.5)	46 (46.0)	56 (93.3)	15 (100.0)
Duration of cardiac arrest, min	22.08 (±22.98)	33.77 (±27.10)	5.46 (±7.96)	50.52 (±48.45)	3.86 (±11.26)	12.55 (±9.33)	15.00 (±3.54)	19.65 (±10.70)	12.12 (±9.05)	6.50 (±2.12)	29.62 (±6.74)	17.95 (±26.91)	NA	21.67 (±7.48)
eCPR	0 (0.0)	4 (8.7)	0 (0.0)	9 (20.9)	0 (0.0)	5 (5.6)	1 (11.1)	8 (12.1)	1 (3.4)	0 (0.0)	0 (0.0)	4 (4.0)	2 (3.3)	0 (0.0)
Mechanical circulatory support	8 (34.8)	9 (19.6)	12 (17.9)	23 (48.9)	8 (36.4)	76 (63.9)	6 (66.7)	18 (27.3)	8 (27.6)	0 (0.0)	19 (26.0)	17 (17.0)	6 (10.0)	0 (0.0)
IABP	1 (4.3)	4 (8.7)	12 (17.9)	1 (2.1)	8 (36.4)	61 (51.3)	6 (66.7)	18 (27.3)	8 (27.6)	0 (0.0)	19 (26.0)	17 (17.0)	6 (10.0)	0 (0.0)
Impella	7 (30.4)	5 (10.9)	0 (0.0)	22 (46.8)	0 (0.0)	34 (28.6)	3 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ECMO	1 (4.3)	11 (23.9)	0 (0.0)	21 (44.7)	3 (13.6)	8 (6.7)	6 (66.7)	7 (10.6)	1 (3.4)	0 (0.0)	1 (1.4)	3 (3.0)	18 (30.0)	0 (0.0)
Vasopressor use	20 (90.9)	37 (80.4)	66 (98.5)	42 (89.4)	17 (77.3)	67 (56.3)	9 (100.0)	55 (83.3)	29 (100.0)	15 (65.2)	55 (85.9)	96 (96.0)	52 (86.7)	4 (26.7)
Inotropes use	10 (45.5)	23 (50.0)	62 (92.5)	34 (72.3)	19 (86.4)	93 (78.2)	9 (100.0)	37 (57.8)	29 (100.0)	14 (60.9)	43 (67.2)	89 (89.0)	54 (90.0)	15 (100.0)
Calcium sensitizer use	2 (9.1)	11 (23.9)	15 (22.4)	13 (27.7)	0 (0.0)	25 (21.2)	0 (0.0)	22 (33.8)	2 (6.9)	6 (26.1)	1 (1.4)	0 (0.0)	12 (20.0)	5 (33.3)
Mechanical ventilation	21 (95.5)	26 (56.5)	41 (61.2)	37 (78.7)	2 (9.1)	79 (66.4)	9 (100.0)	47 (72.3)	28 (96.6)	6 (26.1)	39 (53.4)	96 (96.0)	42 (70.0)	6 (40.0)

Continuous variables are shown as mean (±standard deviation); binary variables are shown as counts (frequencies). BMI – body mass index; eCPR- extracorporeal cardiopulmonary resuscitation; ECMO – extracorporeal membrane oxygenation; IABP – intra-aortic balloon pump

more likely to be recognized in Non-European hospitals. Development of CS remains a particular clinical concern in elderly patients, as multiple studies have identified age as an independent predictor of poor outcomes^{10,14}. The previous studies assessing the outcome of elderly patients with CS complicating AMI reported a wide range of mortality rates, from 55% to 78% (ref.^{10,15,16}). Better cardiovascular prevention, and/or near-universal access to high quality healthcare might contribute to generally higher survival and explain higher age at presentation in European patients, as well as different age structures and life expectancies in European vs. Non-European patients.

Representation of females in the previous CS shock studies accounted for 26-37% (ref.^{4,9,17}). As part of IABP-SHOCK II trial substudy, women had a higher risk profile and seemed to undergo suboptimal treatment in comparison to men, nonetheless no higher mortality rates in short and long-term follow-up for women were observed^{18,19}. Contrary, in other studies, both in-hospital and 12-month mortality following MI were significantly higher in women. Also, women experienced CS more often than men²⁰. Interestingly, we observed much higher likelihood of female sex in CS patients treated at Non-European hospitals in our cohort, and we may speculate whether there might be an underdiagnosis of females with CS in Europe.

Patients with a previous myocardial infarction were more likely to be treated for CS in Non-European hospitals. In contrast, CS associated with acute heart failure was more likely seen in European centers. This might be an effect of sufficient and high-quality access to revascularization procedures and post-ACS care, including antiplatelet therapy and statins, in European countries; so that patients with ACS treated in European countries might be more likely to survive the initial event and to develop heart failure/CS at a later stage.

Vasopressors are used in the management of patients with CS due to their favorable hemodynamic effect, nevertheless they do not target the underlying problem, while only artificially raising blood pressure. Besides symptomatic improvement, however, there is no compelling evidence suggesting a survival benefit of inotropes and vasopressors²¹. In contrast, MCS might correctly target the underlying problem, which is severe impairment in heart function, allowing the recovery of the heart and the reduction of inotropes/vasopressors use with their detrimental effects²². However, MCS utilization has yet to show a favorable impact on survival probabilities^{7,23,24}.

CS treatment incurs substantial resource use and costs. MCS is usually not available in low-income countries due to cost restrictions, as well as long-term devices are almost always not affordable²⁵. Inadequate access to MCS in majority of Non-European countries was apparent in our cohort. Whereas no major difference was observed in terms of IABP use, significantly higher incidence of Impella or extracorporeal membrane oxygenation insertion use was documented in European patients. Perhaps, this might be the reason why vasopressor use was lower in European countries. Although the benefit of MCS in the treatment of CS has not yet been proven, there is

no justification for marginalizing patients not treated in the EU from the latest advances in CS management; and therapeutic advances for CS should be evaluated in all patients, irrespective of region of treatment.

Despite advances in revascularization and MCS, CS mortality is still significantly high, both in European and non-European countries. Gaps in evidence are extensive and relate to the definition, phenotype diversity and management. These gaps might contribute to a large geographical variability in clinical care, including the use of hemodynamic monitoring and timely deployment of MCS (ref.²⁶).

Limitations

This study has several limitations. First, no central adjudication of the CS diagnoses was performed. CS, the only inclusion criterion, was defined at the discretion of the local investigator to avoid a preselection of patients. Second, as with all non-randomized data, we cannot exclude an impact of residual or unmeasured confounders. Third, as this study was designed to retrospectively collect the epidemiologic data of CS patients across the globe, not all relevant variables related to CS could be acquired. Fourth, the follow-up was different between patients treated at European vs. Non-European hospitals, which might have had an impact on the observed outcome.

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