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1 **The association of chronic health status and survival following ventricular**
2 **fibrillation cardiac arrest: Investigation of a primary myocardial mechanism.**

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30 **Abstract**

31 *Introduction:* Quantitative waveform measures are a surrogate of the acute physiological
32 status of the myocardium and predict survival following ventricular fibrillation out-of-
33 hospital cardiac arrest (OHCA). We investigated whether the amplitude spectrum area
34 (AMSA) waveform measure mediates the adverse relationship between increasing burden of
35 chronic health conditions and lower likelihood of survival.

36

37 *Methods:* We performed a cohort investigation of persons ≥ 18 years who suffered
38 ventricular fibrillation OHCA between 2008-2015 in a metropolitan emergency medical
39 service (EMS) system. The count of chronic health conditions was determined using the
40 Charlson Comorbidity Index (CCI). AMSA was calculated just prior to the initial shock. We
41 used multivariable logistic regression to assess the relationship between CCI and survival-to-
42 discharge in models first without and then with AMSA to determine the extent to which
43 AMSA attenuated the CCI-survival association.

44

45 *Results:* Of the 716 eligible patients, 422/716 (59%) had at least one chronic health condition;
46 21.8% with one, 19.6% with two, 10.3% with 3, and 7.3% with ≥ 4 . Survival-to-discharge
47 was 45% (324/716). In the multivariable model adjusted for traditional Utstein
48 characteristics, increasing CCI was associated with lower odds of survival (Odds ratio (OR)
49 (95% confidence interval) =0.82 [0.72, 0.93] for each additional chronic health condition).
50 The addition of AMSA to the model only modestly attenuated the CCI-survival association
51 (OR=0.85 [0.74,0.98]).

52

53 *Conclusion:* The waveform measure AMSA – a surrogate for the physiological status of the
54 myocardium – mediated only a modest portion of the association between increasing burden

55 of chronic health conditions and lower likelihood of survival following ventricular fibrillation

56 OHCA.

57

58 **Introduction**

59

60 Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality worldwide ¹.

61 Considerable programmatic and research efforts are directed toward improving resuscitation.

62 A key to improving outcomes is to understand the factors that influence resuscitation. The

63 Utstein data elements, which include demographic, circumstance, and resuscitation care

64 characteristics predict outcome but collectively only account for a modest portion of outcome

65 variability ^{2 3}.

66

67 Increasing evidence has indicated that the burden of chronic health conditions can adversely

68 influence prognosis ⁴⁻⁶. The reasons for this association are not well-understood. One

69 hypothesis is that chronic health conditions directly affect the myocardial substrate, making

70 patients with excess chronic health conditions less responsive to treatment and hence less

71 likely to survive following ventricular fibrillation (VF) OHCA. There is however a lack of

72 rigorous investigation evaluating the relationship between chronic health conditions and the

73 heart's physiologic status during VF OHCA ⁷⁻¹⁰. Identifying the mechanism(s) by which

74 chronic health conditions influence prognosis can improve scientific understanding of

75 resuscitation, help explain outcome differences across populations or geographies, and

76 potentially provide the basis to improve care.

77

78 Quantitative measures of the VF waveform are dynamic and predict outcome over the course

79 of resuscitation ¹¹⁻¹⁴. These measures can correspond to the heart's ischemic burden and

80 provide an assessment of energy status of the myocardial substrate^{15 16}. Thus, as a surrogate

81 for myocardial status, quantitative waveform measures provide a means to evaluate whether

82 chronic health conditions might confer excess risk through a primary myocardial mechanism.

83 We used the waveform measure amplitude spectrum area (AMSA) as it predicts both shock-

84 specific ECG outcome (return of organized rhythm) and clinical outcome (return of
85 circulation and survival to hospital discharge) across different human VF populations¹¹⁻¹⁴. To
86 test this theory, we hypothesized that waveform measures account for the adverse association
87 between increasing burden of chronic health conditions and outcome following VF OHCA.

88

89 **Methods**

90 *Design, study population, and setting:*

91 We performed a cohort investigation of persons 18 years or older who suffered non-traumatic
92 OHCA and presented with ventricular fibrillation between January 1, 2008 and December 31,
93 2015 in a large metropolitan emergency medical service (EMS) system. Because the
94 investigation required ECG information prior to the initial shock from the defibrillator
95 recording, we a-priori excluded cases that received a shock from a non-EMS defibrillator i.e.
96 public access defibrillator or law enforcement – as these would not routinely be available for
97 review and analysis. We also excluded cases where the EMS provided the initial shock but
98 the EMS defibrillator download was unavailable or technically not adequate (corrupted or
99 missing ECG).

100

101 The EMS system serves a population of approximately 1.3 million persons residing in urban,
102 suburban, and rural settings covering an area of about 2000 square miles. The EMS is a two-
103 tiered system. The first tier is emergency medical technician-trained firefighters who provide
104 basic life support and are equipped with automated external defibrillators. The second tier is
105 paramedics trained in advanced life support including manual rhythm interpretation and
106 defibrillation, intubation, and intravenous medication therapies. Resuscitation care is based
107 on the American Heart Association guidelines¹⁷. Patients who are resuscitated are
108 transported to area hospitals, each equipped with coronary catheterization and intensive care

109 services. Hospital-based care is at the discretion of the treating physician ¹⁸. The
110 institutional review boards at the University of Washington and Public Health – Seattle &
111 King County approved the study.

112

113 *Data collection and definitions:*

114 The EMS system maintains an ongoing registry of all EMS-treated cardiac arrests.
115 Information about demographics, circumstances, care, and outcome is ascertained using
116 emergency dispatch, EMS, defibrillator, hospital and death records. The information is
117 organized according to the Utstein Guidelines for reporting OHCA ³. Investigators abstract
118 information from dispatch and EMS records blinded to outcome status.

119

120 Information about pre-existing, clinically-recognized chronic health conditions was collected
121 from the EMS reports ¹⁹. Information from EMS records is available for all treated patients
122 and has a fair to good kappa with hospital-based information. Inter-reviewer reliability for
123 selected conditions has revealed a high level of agreement. The complete abstraction form
124 including health conditions and chronic medication treatments has been previously published
125 ⁶. Chronic conditions were tallied to generate the Charlson Comorbidity Index (CCI) and
126 categorized into 5 groups (0, 1, 2, 3 or ≥ 4) with higher numbers indicating greater burden of
127 chronic health conditions ²⁰. The primary outcome was survival, as confirmed by vital status
128 at hospital discharge.

129

130 *ECG*

131 Real-time ECG tracings were collected from the EMS defibrillator recording. ECGs were
132 collected from MRx and ForeRunner 3 (Philips Healthcare, Bothell, WA) defibrillators and
133 from Lifepak 12 and Lifepak 15 (Physio-Control, Redmond, WA) defibrillators. MRx ECGs

134 were analyzed at their original sample rate of 250 Hz, ForeRunner 3 ECGs were resampled
135 from 200 Hz to 250 Hz, and Lifepak ECGs were resampled from 125 Hz to 250 Hz. All ECG
136 segments were bandpass-filtered from 4 – 48 Hz using a 4th-order Butterworth filter with a
137 zero-phase implementation

138

139 *AMSA Calculation*

140 We extracted a 5-second VF ECG epoch from each patient during the CPR pause
141 immediately before the first shock. Pauses in CPR were confirmed by review of the chest
142 impedance signal. We used these 5-second ECG epochs to generate the amplitude spectrum
143 area (AMSA), a frequency-domain quantitative waveform measure. AMSA was calculated as
144 $AMSA = \sum_{m=4Hz \cdot N/f_s}^{48Hz \cdot N/f_s} (X_m f_m)$, where X_m are the one-sided Discrete Fourier Transform
145 magnitudes calculated from a Hanning-windowed VF ECG segment of N samples, f_m are the
146 frequency values (in Hz) corresponding to each X_m magnitude, and f_s is the sampling rate.¹⁶
147 ²¹⁻²³ As AMSA is calculated using the sum of the products of each frequency value and its
148 corresponding magnitude, a VF ECG segment with more high-frequency content will
149 typically have a higher AMSA value. Data extraction and processing were performed using
150 MATLAB R2017a (The Mathworks Inc, Natick, MA).^{24 25}

151

152

153 *Statistical analysis:*

154 We used descriptive statistics to summarize categorical variables as proportions, and
155 continuous variables as mean with standard deviation for normal distribution or as median
156 with interquartile range for non-normal distribution. We conducted analyses to understand
157 whether the association between chronic health conditions and survival was mediated by the
158 AMSA waveform measure. We used logistic regression to determine the unadjusted

159 association between Utstein parameters, chronic health conditions, and AMSA and outcome.
160 We constructed a multivariable model that included the Utstein predictors and the CCI with
161 CCI being modeled as a continuous categorical variable. We then added AMSA quartile
162 modeled as a continuous categorical variable to the multivariable model. Given the
163 hypothesis that chronic conditions affect prognosis through a cardiac mechanism, we
164 expected that addition of AMSA to the model would attenuate the association between
165 chronic health conditions and outcome. We measured this contribution on a percentage basis
166 using the equation: $1 - (\beta_{\text{chronic health conditions adjusted}} / \beta_{\text{chronic health conditions baseline}})$, where
167 β are the multivariable logistic model coefficients.²⁸

168

169 Finally, we assessed for differences in the association between chronic health conditions,
170 AMSA, and outcome among subgroups defined by witness status, age (≥ 65 versus < 65
171 years), and sex by including an interaction (cross-product) term between chronic health
172 condition group and the covariates of interest. All tests were performed using STATA/SE
173 14.2 (Lakeway Drive, TX, USA). A p-value < 0.05 was considered statistically significant.

174 **Results**

175 During the study period, 1611 persons had OHCA with an initial rhythm of VF. Of
176 these 1611, 194 (12%) received initial defibrillation by non-EMS AED (public access or law
177 enforcement) and were a-priori ineligible. Of the 1417 eligible patients, 554 (39%) either did
178 not have an EMS defibrillator download or the recording was not technically sufficient, and
179 150 patients (11%) had no information regarding chronic health conditions, leaving 716 for
180 the primary study cohort (Figure 1). Compared to the primary study cohort, eligible patients
181 who were excluded were more likely to experience the arrest in a public location and receive
182 bystander CPR (Table 1). Overall survival to discharge was 324/716 (45%) and did not
183 differ between included and excluded patient groups.

184

185 Chronic health conditions as calculated per the CCI were observed in the majority of patients
186 422/716 (59%); 21.8% had one chronic health condition, 19.6% had two, 10.3% had 3, and
187 7.3% had 4 or more chronic health conditions. Table 2 presents the distribution of covariates
188 according to the chronic health condition groups. As chronic health conditions increased in
189 number, patients were increasingly older, experienced cardiac arrest in non-public area, and
190 had longer EMS response intervals ($p < 0.05$ for trend). AMSA decreased as CCI increased
191 ($p < 0.05$), whereas increasing AMSA quartiles were associated with younger age, public
192 location, witnessed status, and bystander CPR performance ($p < 0.05$ for trend) (Table 3).

193

194

195 Table 4 presents the results of the logistic regression models. In unadjusted models,
196 increasing CCI was associated with a decreasing likelihood of survival (trend odds ratio [OR]
197 = 0.79 [CI=0.70-0.89], $p < 0.001$), while increasing quartile of AMSA was associated with an
198 increasing likelihood of survival (trend OR = 1.31 [1.24-1.37], $p < 0.001$). In the

199 multivariable model that adjusted for Utstein predictors, increasing CCI remained associated
200 with a lower likelihood of survival (trend OR=0.82 (0.72-0.93], p=0.003). When AMSA
201 quartile was added to the multivariable model, the association between CCI and survival was
202 attenuated only slightly (trend OR = 0.85 [0.74-0.98]). The beta for chronic health conditions
203 was -0.202 without AMSA and -0.163 with AMSA in the multivariable model, indicating
204 AMSA mediates 19% $(1 - [\beta_2/\beta_1]) \times 100$ of the association between chronic health
205 conditions and survival.

206

207 In sensitivity analyses, we did not observe an interaction between chronic health conditions
208 and survival according to subgroup characteristics that had an apparent association with
209 survival outcome (Table 4), including witnessed arrest status (p for interaction=0.69), age (p
210 for interaction=0.41), or sex (p for interaction=0.43).

211

212 **Discussion**

213 In the present cohort investigation of OHCA due to VF, an increasing burden of chronic
214 health conditions was associated with a lower likelihood of survival after adjustment for
215 traditional Utstein elements describing demographic, circumstance, and response
216 characteristics. When the model also incorporated AMSA, the adverse association of chronic
217 health conditions was attenuated only modestly and retained its independent association with
218 survival. Collectively, the results suggest that myocardial substrate as measured by the
219 AMSA waveform measure does not primarily mediate the association between an increasing
220 burden of chronic health conditions and lower likelihood of survival following VF arrest,
221 suggesting that other alternative mechanisms should be considered.

222

223 Prior research has demonstrated that the Utstein elements are important predictors but are not
224 sufficient to explain outcome differences within or across systems, and collectively account
225 for only a modest proportion of the variability in survival ^{2,29}. The results of current and prior
226 investigations indicate that incorporating chronic health conditions can improve prediction.
227 In the present study, an increasing burden of chronic health conditions was associated with a
228 reduced likelihood of survival in a dose-dependent fashion. The question then is what
229 mechanisms might mediate this adverse risk given that all patients in the current cohort
230 presented with VF ventricular fibrillation in a model that was adjusted for Utstein
231 characteristics?

232

233 In this study, we investigated whether a primary myocardial mechanism might explain the
234 association between comorbidity and OHCA outcome. We hypothesized that chronic health
235 conditions might affect the intrinsic myocardial expression of VF. Specifically, we used the
236 AMSA quantitative waveform measure derived from the ECG captured just prior to the initial

237 shock. Previous research suggests that waveform measures such as AMSA might serve as a
238 surrogate for coronary perfusion pressure and myocardial energy during resuscitation^{7,8}.
239 Indeed we observed a strong and independent relationship between increasing AMSA and a
240 greater likelihood of survival. However, inclusion of AMSA in the multivariable model
241 accounted for only a modest proportion of the adverse relationship between chronic health
242 conditions and outcome, suggesting that other mechanisms account for the association.

243

244 Other mechanisms might include variability in pre-hospital emergency medical services
245 (EMS) interventions, which could differ according to chronic health status. Although the
246 Utstein elements include categorical EMS measures, there may be differences in quantitative
247 aspects of care such as the timing and quality of bystander and EMS CPR. Alternatively,
248 hospital care may differ according to the burden of chronic health conditions, and could
249 influence the types and extent of hospital intervention and support.

250

251 The current study has limitations. Specifically we were not able to evaluate more detailed
252 potential mediators to include the aforementioned quantitative prehospital measures of
253 resuscitation or in-hospital care. We used a clinical outcome (survival) that is several steps
254 removed from the initial waveform measure. The use of more proximal outcome could
255 reveal different relationships among CCI, AMSA, and intermediate outcomes such as
256 organized rhythm following the shock. The study used an observational design. Thus
257 caution must be exercised in attributing cause-and-effect outcome relationships as it relates to
258 chronic health conditions and AMSA, though these findings were adjusted for potential
259 confounders. Chronic health conditions in this study were ascertained by EMS providers.
260 Although this approach may underestimate the prevalence of comorbidity, it captures this
261 information in all patients, including those who did not survive to hospital admission and

262 whose comorbidities might not otherwise be known. Moreover the accuracy of this
263 methodology has been validated when compared with hospital-sourced information.¹⁹ The
264 current study evaluates cumulative comorbidity as measured by the Charlson Index and does
265 not investigate a specific comorbidity, its influence on outcome, or whether this relationship
266 may be mediated by primary cardiac mechanism as measured by the AMSA waveform.
267 Indeed specific comorbidities may have distinct mechanisms influencing outcome. We used
268 AMSA as a surrogate of myocardial status given this waveform measure is well-tested as a
269 predictor of outcome. Other waveform measures, or alternative surrogates for myocardial
270 status, may have produced different results. Finally, the results come from a mature
271 metropolitan EMS system that achieves a relatively high survival such that the results may
272 not be generalizable to all communities. These limitations should be balanced with the
273 investigation's strengths; a well-characterized cohort of persons with VF arrest that
274 incorporated quantitative waveform measures to evaluate novel relationships potentially
275 responsible for resuscitation mechanisms.

276

277 **Conclusions**

278 An increasing burden of chronic health conditions was associated with a lower likelihood of
279 survival following VF OHCA independent of traditional Utstein predictors. The quantitative
280 waveform measure AMSA – a surrogate for the physiological status of the myocardium –
281 accounted for only a modest portion of the association between chronic health conditions and
282 outcome, suggesting other mechanisms are likely responsible for this association. Future
283 study should investigate alternative mechanisms to account for this association as a means to
284 understand heterogeneity of outcome and potentially help improve resuscitation care.

285

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293

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400

Figure 1 : Flow chart of the study population

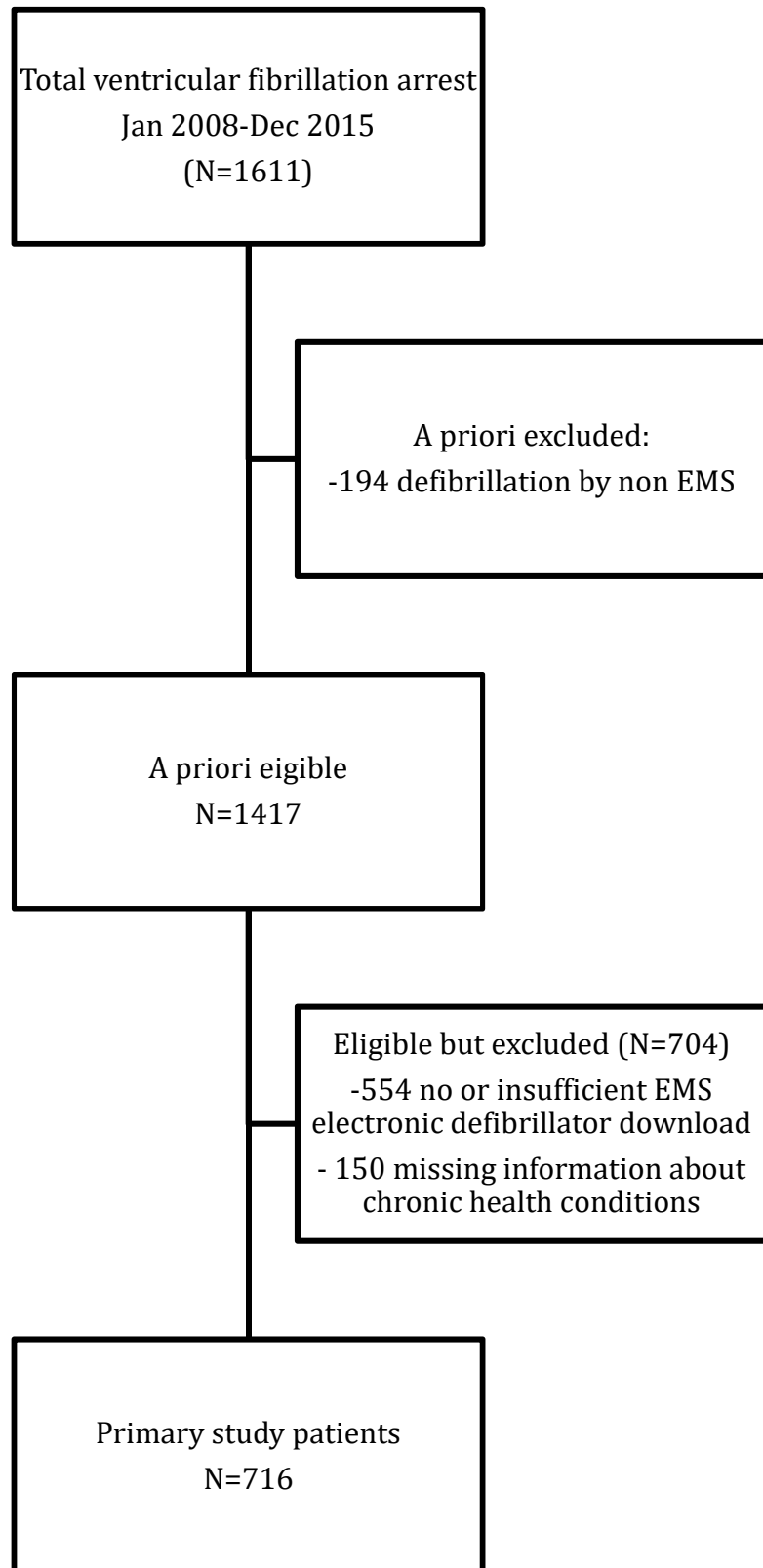


Table 1. Comparison between primary study patients and those eligible but excluded

	Primary study cohort N=716	Eligible Excluded N=704	
Age, years (SD)	61.8 (15.5)	63.8 (14.5)	0.10
Male gender, n (%)	540 (75)	546 (78)	0.35
Public location, n (%)	174 (24)	249 (35)	<0.001
Witnessed, n (%)	553 (77)	530 (75)	0.39
Bystander CPR, n (%)	515 (72)	442 (63)	<0.001
EMS response interval>5 min n (%)	350 (50)	338 (52)	0.44
Cardiac etiology, n (%)	663 (93)	634 (90)	0.09
CCI=0	294 (41)	252 (40)	0.06
CCI=1	156 (22)	125 (20)	
CCI=2	140 (20)	119 (19)	
CCI=3	74 (10)	57 (9)	
CCI≥4	52 (7)	75 (12)	
AMSA (SD)	7.31 (4.0)	7.52 (3.8)	0.28
Hospital survival, n (%)	324 (45)	316 (45)	0.89

Table 2 : Utstein and AMSA covariates according to chronic health categories (SD= standard deviation, CPR= cardiopulmonary resuscitation, CCI= Charlson comorbidity index, p-value* for trend)

	Charlson Comorbidity Index					p-value*
	CCI=0	CCI=1	CCI=2	CCI=3	CCI≥4	
	N=294	N=156	N=140	N=74	N=52	
Age years (SD)	56.9 (16.3)	65.4 (15.3)	64.1 (12.8)	65.6 (13)	67.4 (14.5)	<0.001
Male gender, n(%)	222 (76)	121 (78)	102 (73)	55 (74)	40 (77)	0.83
Public location, n(%)	87 (30)	39 (25)	33 (24)	13 (18)	2 (4)	<0.001
Witnessed, n(%)	223 (76)	121 (78)	117 (84)	59 (80)	33 (63)	0.74
Bystander CPR, n(%)	217 (74)	107 (69)	101 (72)	54 (73)	36 (69)	0.61
EMS Response >5 min, n(%)	129 (45)	77 (51)	72 (53)	42 (58)	30 (60)	0.009
Cardiac etiology, n(%)	269 (92)	146 (94)	134 (96)	68 (92)	46 (88)	0.99
AMSA mean (SD)	7.5 (3.9)	7.6 (4.1)	7.5 (4.4)	6.7 (3.5)	5.8 (2.8)	0.02

Table 3 : Utstein and chronic health conditions according to AMSA quartiles. (* dichotomized according to the median, SD= standard deviation, CPR= cardiopulmonary resuscitation, CCI= Charlson comorbidity index)

AMSA value	AMSA Quartiles				p-value	
	<4.20 N=187	4.20-6.80 N=180	6.80-9.60 N=174	>9.60 N=175		
Age, years (SD)	63.8 (15.2)	62.9 (15.4)	61.9 (16.2)	58.5 (14.9)	0.008	
Male gender, n(%)	149 (80)	138 (77)	124 (71)	129 (74)	0.10	
Public location, n(%)	34 (18)	34 (19)	48 (28)	58 (33)	<0.001	
Witnessed, n(%)	117 (63)	139 (77)	146 (84)	151 (86)	<0.001	
Bystander CPR, n(%)	117 (63)	127 (71)	131 (75)	140 (80)	<0.001	
EMS response >5 min, n(%)	85 (24)	86 (25)	90 (26)	89 (25)	0.46	
Cardiac etiology, n(%)	171 (91)	165 (92)	161 (93)	166 (95)	0.21	
CCI					0.048	
	0	73 (39)	72 (40)	71 (41)	78 (45)	
	1	40 (21)	30 (17)	48 (28)	38 (22)	
	2	33 (18)	42 (23)	27 (16)	38 (22)	
	3	23 (12)	19(11)	19 (11)	13 (7)	
	≥4	18 (10)	17 (9)	9 (5)	8 (5)	

Table 4 : Logistic regression predicting survival at discharge ; (CPR=cardiopulmonary resuscitation ; CCI=Charlson comorbidity index)

	Unadjusted odds ratio of survival			Multivariable odds ratio of survival					
	OR	95% CI	p-value	Utstein-only adjusted			Utstein and AMSA adjusted		
				OR	95% CI	p-value	OR	95% CI	p-value
Age	0.97	(0.96-0.98)	<0.001	0.97	(0.96-0.98)	<0.001	0.97	(0.96-0.98)	<0.001
Male gender	0.75	(0.54-1.06)	0.10	0.69	(0.48-1.0)	0.05	0.75	(0.50-1.11)	0.15
Public location	1.50	(1.06-2.11)	0.02	1.04	(0.72-1.52)	0.82	0.84	(0.56-1.27)	0.41
Witnessed	2.77	(1.89-4.07)	<0.001	2.56	(.70-3.86)	<0.001	1.99	(1.28-3.08)	0.002
Bystander CPR	1.22	(0.87-1.69)	0.25	1.29	(0.89-1.85)	0.18	0.97	(0.65-1.45)	0.89
EMS Response time< 5 min	1.42	(1.05-1.92)	0.02	1.53	(1.10-2.13)	0.01	1.43	(1.01-2.04)	0.045
Cardiac etiology	2.45	(1.30-4.59)	0.005	3.27	(1.60-6.69)	0.001	2.99	(1.39-6.45)	0.005
CCI	0.78	(0.70-0.89)	<0.001	0.82	(0.72-0.93)	0.003	0.85	(0.74-0.98)	0.025
AMSA	1.31	(1.24-1.37)	<0.001	---	----	-----	1.27	(1.20-1.34)	<0.001