Age, sex, and survival following ventricular fibrillation cardiac arrest: a mechanistic evaluation of the ECG waveform

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Abstract

Age, sex, and survival following ventricular fibrillation cardiac arrest: a mechanistic evaluation of the ECG waveform

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Background: Sex-based outcome comparisons in out-of-hospital cardiac arrest (OHCA) have produced mixed results. Sex-based outcomes may depend in part on age, as menopause produces a range of biological effects that may influence resuscitation. We used quantitative measures of the ventricular fibrillation (VF) waveform – a surrogate of the myocardium's acute physiology – to assess whether outcome differences according to sex and age group may be mediated via a biologic mechanism.

Methods: We conducted a retrospective cohort study of adult non-traumatic VF-OHCA patients in King County, Washington between 2008-2020. We used multivariable logistic regression to assess the relationship of outcome (survival to hospital discharge, favorable neurological outcome (Cerebral Performance Category (CPC) 1 or 2), according to sex and age group (<55, ≥55). We determined the proportion of the outcome difference mediated by the waveform

measure by incorporating the VF waveform measures - probability of survival, amplitude spectrum area, frequency, and median peak amplitude individually - into the multivariable model.

Results: Of 1526 VF-OHCA patients, average age was 62 years, and 29% were female. Overall, we observed that younger women were more likely to survive than younger men (survival 67% vs 54%, p=0.02 and favorable neurologic outcome 61% vs 51%, p=0.07), while older women and older men fared more similarly (survival 44% vs 40%, p=0.3 and favorable neurologic survival 39% vs 37%, p=0.7). After adjusting for Utstein characteristics, women <55 compared to men <55 was associated with greater odds of survival to hospital discharge (OR 1.93, 95% CI 1.23-3.09, p=0.005) and favorable neurological survival (OR 1.72, 95% CI 1.10-2.71, p=0.02). In contrast, women ≥55 compared to men ≥55 was not associated with a difference in the odds of survival to hospital discharge (1.19, 95% CI 0.88-1.60, p=0.3) and favorable neurological survival (1.08, 95% CI 0.79-1.46, p=0.7). The added waveform measures mediated some the beneficial association between survival and female sex among those <55: 47% for probability of survival, 25% for amplitude spectrum area, 19% for frequency, and 17% for median peak amplitude.

Conclusions: In this observational cohort study of VF-OHCA, we observed that women <55 years were more likely to survive to hospital discharge and survive with favorable neurological status compared to men <55 years; a sex-based outcome difference not observed among the older age group. VF waveform measures as a surrogate for acute physiologic status of the heart– mediated some, though not all, of the outcome difference.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major cause of mortality worldwide.[1,2] Each year in the United States, approximately 360,000 patients suffer OHCA, many of whom are treated by emergency medical services (EMS) in the United States.[3] Ventricular fibrillation (VF) is a common initial dysrhythmia and associated with a better likelihood of favorable outcome, on average about 30% survive to hospital discharge. [4] Importantly there is a 5-fold variability in outcome across systems, supporting the premise that ventricular fibrillation OHCA (VF-OHCA) is a modifiable condition amenable to improvement.[5,6]

Sex-based differences have been studied across a spectrum of clinical cardiovascular disease, highlighting promising strategies to address biological, socioeconomic, or clinical mechanisms responsible for disparity. Sex-based outcome comparisons in OHCA have produced mixed results. A large multi-center study of OHCA observed that women overall had a lower rate of survival and worse survival predictors, yet younger women had a survival advantage.[7] Importantly, sex-specific pathophysiology of VF-OHCA may depend on age, given that cardiovascular biology changes markedly after menopause. Consistent with this biological hypothesis, a prior investigation observed a survival advantage among young women compared to young men, while older women and men fared similarly.[8] The basis for a potential interaction between sex and age, however, is uncertain; mechanistic understanding could advance strategies to improve resuscitation.

Ventricular fibrillation waveform measures assess the frequency, amplitude, and organizational characteristics of the electrocardiogram (ECG). These measures are associated with the heart's physiologic status, provide a dynamic assessment of the myocardial substrate during OHCA, and

predict clinical outcome.[9,10] Thus, VF waveform morphology may represent a key biological reference point that can help explain survival mechanisms and outcome differences.

In this study, we aim to investigate VF-OHCA survival differences between women and men according to age and to determine whether such outcomes differences may be explained through biological mechanisms represented by VF waveform measures.

Methods

Study Design, Population, and Setting. This investigation is an observational cohort study of adult patients (age 18 years or older) treated for by emergency medical services (EMS) in King County, WA (excluding Seattle) for VF-OHCA between 2008 and 2020. Inclusion required a defibrillator recording with ECG and transthoracic impedance signal before the first shock used to identify a 3-second ECG segment without CPR. Patients were excluded if they received an initial shock by public access or police defibrillator prior to EMS arrival, had a do-not-resuscitate directive, or were incarcerated. Patients were also excluded if there was ECG artifact (i.e. from pacemaker or implantable cardioverter defibrillator (ICD)).

Greater King County (excluding the City of Seattle) has a population of 1.5 million persons who reside in urban, suburban, and rural settings. The EMS is a two-tiered system, initiated by 9-1-1 call. Resuscitation follows the American Heart Association Guidelines.[11] First-tier EMTs provide cardiopulmonary resuscitation (CPR) and use automated external defibrillators (AEDs). Second-tier paramedics are trained in advanced cardiac life support and use manual defibrillators.

Patients are transported to one of 14 hospitals equipped with coronary intervention and ICU capability.

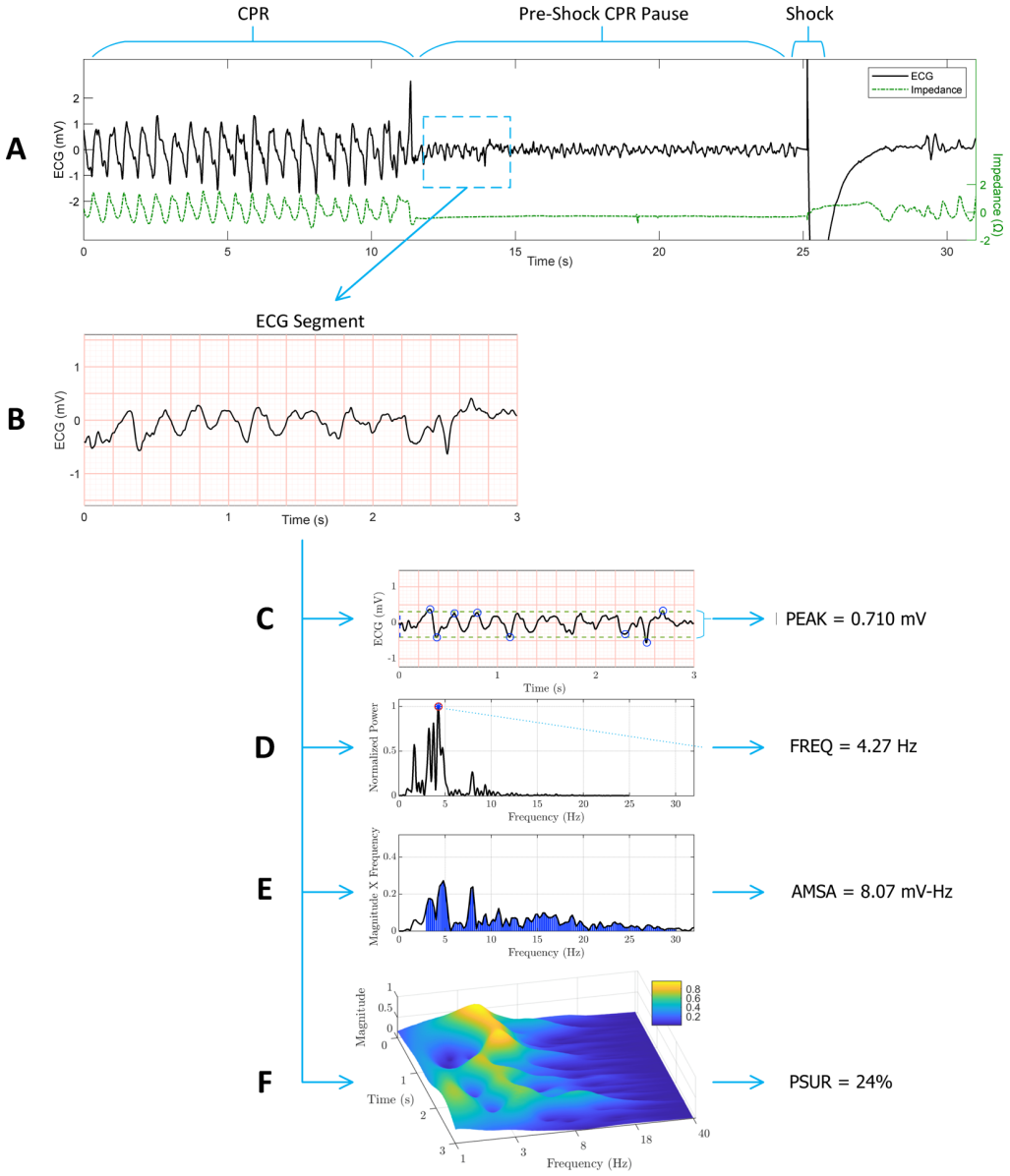
The study was approved by the University of Washington Institutional Review Board. Because the investigation was observational and considered minimal risk, the requirement for consent was waived. This study was conducted in accordance with STROBE guidelines.[12]

Data Collection and Definitions. The Division of Emergency Medical Services (EMS) of Public Health - Seattle and King County maintains an ongoing comprehensive clinical registry of OHCA as part of a program of quality assurance.[13] Active surveillance identifies each case. The review process uses information from emergency dispatch, EMS, defibrillator, hospital, and death records. The defibrillator recording includes the real-time ECG, impedance, and audio. Using a uniform data abstraction form supported by a data dictionary, trained coordinators review and code demographic, arrest circumstance, care and outcome information according to the Utstein template.[14] Etiology is determined based on review of EMS, hospital, and death records. Because the variables of interest were sex and age in particular, as related to pre- and post-menopause, we modeled four primary exposure groups: men <55 years, women <55 years, men ≥55 years, women ≥55 years.

VF Waveform Measures. MATLAB (Mathworks, Natick, MA) software was used to review the ECG and transthoracic impedance signals from the defibrillator recording to extract a CPR-free, 3-second ECG segment immediately prior to the initial shock. Defibrillator models included Forerunner 3, Heartstart MRx (Philips Healthcare, Bothell, WA), Lifepak 12, and Lifepak 15 (Stryker Physio-Control, Redmond, WA). ECG sampling rates ranged from 125 to 250 Hz across devices; signals at an original sampling rate < 250 Hz were resampled to 250 Hz. We calculated

4 VF waveform measures: median peak frequency (FREQ), median peak amplitude (PEAK), amplitude spectrum area (AMSA), and probability of hospital survival (PSUR) (Figure 1).[10,15]

Figure 1. VF waveform analysis



From (A) the defibrillator recording, we select (B) a 3-second ECG segment selected from pre-shock period with no ongoing CPR for analysis. The waveform from this segment is analyzed for (C) median peak amplitude (PEAK, mV), (D) peak frequency (FREQ, Hz), (E) amplitude spectral area (AMSA, mV-Hz), and (F) algorithm generating the probability of survival, based on magnitude, frequency and time.

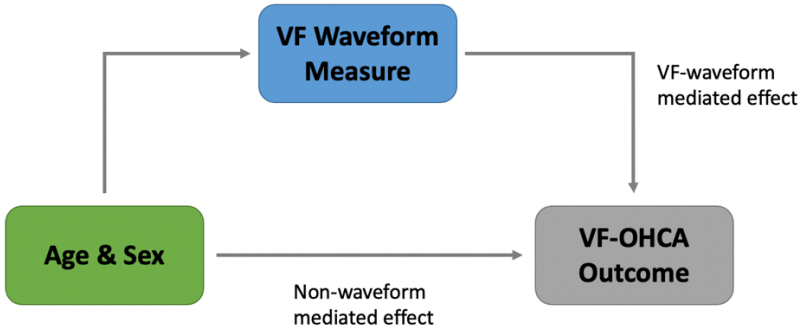
Abbreviations: ECG = Electrocardiogram; PEAK = Median Peak Amplitude; FREQ = Peak Frequency; AMSA = Amplitude Spectral Area; PSUR = probability of Survival.

Outcome. The primary outcome was survival to hospital discharge. The secondary outcomes were survival with favorable neurological survival as determined by the Cerebral Performance Category (CPC 1 or 2) and sustained return of spontaneous circulation (ROSC).

Statistical Analysis. We used descriptive statistics to summarize characteristics according to sex and age group. Continuous variables were compared using F-tests, whereas categorical variables were compared with the chi-square test.

To evaluate the association among the age-sex groups and outcome, we used multivariable logistic regression, modeling survival to hospital discharge according to age-sex group using men <55 as the referent. We repeated analyses using the outcomes of favorable neurological survival (survival with CPC 1 or 2) and sustained ROSC. Models adjusted for cardiac etiology, witness status (unwitnessed, witnessed by bystander, witnessed by EMS), public location, bystander CPR, and the time to first EMS response (time interval from dispatch to scene arrival). Models evaluating the potential mechanism represented by the waveform included individual waveform measures to determine if its addition (adjustment) to the multivariable model attenuates the association of sex according to age group. In sensitivity analyses, we used ages 50 and 60 years as the age threshold to determine the age groups. We then performed a causal mediation analysis, adding each VF waveform measure as a potential mediator (Figure 2). We used the R package *mediation* to calculate the mediated and non-mediated effects of each VF waveform measure.[16–18] Standard statistical software (R version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis.[19]

Figure 2. Model with VF waveform measure as mediator.



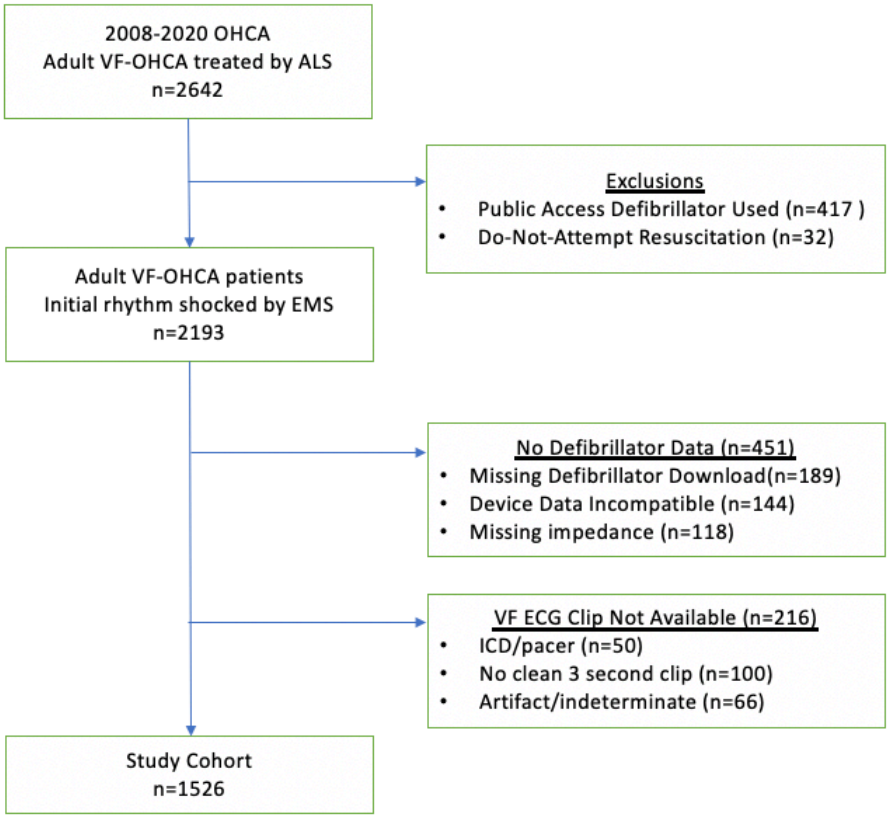
Abbreviations: VF = Ventricular Fibrillation. OHCA = Out-of-Hospital Cardiac Arrest

Results

Of the 2193 total VF-OHCA patients receiving a shock from EMS, 667 did not have adequate defibrillator recording, leaving a total of 1526 VF-OHCA patients for analysis (Figure 2). Overall average age was 62 years, and 29% were female (Table 1). Women comprised 26% among those < 55 years and 21% among those ≥55. Among those <55 years, women were younger, less likely to have an arrest due to a cardiac etiology, and less likely to experience arrest in a public location (Table 1). Among those ≥55 years, women were older and have the arrest witnessed by EMS. When comparing the VF measures, women on average had more favorable measures compared to men among the younger and older age groups (Table 1).

With regard to outcomes, we observed that younger women fared better than younger men (survival 67% vs 54%, p=0.02 and favorable neurologic outcome 61% vs 51%, p=0.07), while

Figure 3. Patient Flow Diagram



Abbreviations: VF = Ventricular Fibrillation; OHCA = Out-of-Hospital Cardiac Arrest; EMS = Emergency Medical Services; ICD = Implantable Cardioverter Defibrillator

older women and older men fared more similarly (survival 44% vs 40%, p=0.3 and favorable neurologic survival 39% vs 37%, p=0.7).

After adjusting for Utstein characteristics, women <55 compared to men <55 was associated with greater odds of survival to hospital discharge (OR 1.93, 95% CI 1.23-3.09, p=0.005) and favorable neurological survival (OR 1.72, 95% CI 1.10-2.71, p=0.018) (Table 2). In contrast, there was no difference in odds of survival to discharge (OR 1.19, 95% CI 0.87-1.62, p=0.3) or

favorable neurological survival (OR 1.07, 95% CI 0.78-1.46, p=0.7) for women > 55 compared to men >55. Similar results were observed when ROSC was used as the outcome.

In most models, the addition of an individual waveform measure modestly attenuated the favorable outcome association for younger women compared to younger men (Table 2). The addition of PSUR, however, attenuated the odds ratio from 1.93 (95% CI 1.23-3.09, p=0.005) to 1.54 (95% CI 0.94-2.56, p=0.091) for survival, 1.72 (95% CI 1.10-2.71, p=0.018) to 1.32 (95% CI 0.81-2.17, p=0.272) for favorable neurological survival, and 1.96 (95% CI 1.17-3.39, p=0.013) to 1.64 (95% CI 0.96-2.91, p=0.080) for ROSC.

In causal mediation analysis, the VF waveform measures mediated some of the association between age-sex group and outcomes. Among women and men <55, we observed that each waveform measure mediated the association between age and sex group and survival by 43% for PSUR, 27% for AMSA, 21% for FREQ, and 15% for PEAK. With the favorable neurologic survival, the proportion mediated was higher: 55% for PSUR, 31% for AMSA, 26% for FREQ, and 26% for PEAK.

In sensitivity analyses that used age groups stratified by age 50 or age 60 (instead of age 55), the results were similar.

Discussion

Summary of pertinent results

In this observational cohort study of VF-OHCA, we observed that women <55 years were more likely to achieve ROSC, survive, and survive with favorable neurological status, compared to men <55 years after adjustment for Utstein demographic, circumstance, and care outcome predictors. In contrast, we did not observe outcome differences between older women and older men in unadjusted or adjusted comparisons. When adjusted for the VF waveform measures, the survival advantage among younger women was attenuated. However, this surrogate biological marker of cardiac physiology did not appear to be the major mechanism for outcome differences, suggesting that other factors may contribute to resuscitation outcome differences between younger women and men.

Age, sex, VF-OHCA outcomes background

The incidence of heart disease is different between men and women with the onset about a decade later on average in women. The mechanisms for this age-based difference are complex but thought to be related to the cardiovascular protective effects of estrogens. With regard to OHCA incidence, hormone profiles are dynamically associated with risk among women with long QT. When considering resuscitation, female hormone profiles may affect defibrillation threshold, antiarrhythmic medication effects, contractility, coagulation, electrical excitability. However, little is known about sex-specific resuscitation outcomes as they relate to pre- and post-menopause status. In a study of in-hospital cardiac arrest involving shockable and nonshockable rhythms, women were more likely to be resuscitated and survive, an association

driven by the survival advantage among younger women.[20] In a study restricted to VF-OHCA, women were more likely to be resuscitated, but no more likely to survive.[21] A small sample size prevented an evaluation of age-specific differences.

In the current study, we observe a survival advantage for younger women compared to younger men, but no sex-specific outcome difference among older ages. The finding is not explained by differences in Utstein predictors which include arrest circumstances (witness, location) and basic prehospital care health services (bystander CPR, EMS response interval). Nor was the difference explained by downstream hospital-based interventions to include targeted temperature management and coronary angiography. The result is potentially consistent with distinct physiologic profiles that may respond differentially to resuscitation care corresponding to pre- and post-menopause status.

VF waveforms

We sought to use measures of the VF waveform to understand if the outcome differences between younger women and men might be due to the heart's acute biologic circumstance. Quantitative waveform measures correspond to myocardial cellular adenosine triphosphate (ATP) levels and in turn predict clinical outcomes.[10,15] Moreover, the waveform measures have been used to help explain and validate the biologic mechanism of early CPR.[18]

In the current study, we observed that women and in particular younger women had more robust waveform measures immediately prior to the initial shock and that these measures are strong predictors of outcome. Yet adjustment for the waveform measures only partially attenuated the outcome differences between younger women and men. In particular, the proportion mediated by

PSUR between younger women and men was 43%, with other measures producing smaller degree of attenuation. The PSUR measure incorporates magnitude, time, and frequency of the waveform, capturing a 3-dimensional perspective of cardiac activity over time and may be a higher fidelity reflection of the heart's dynamic physiology. These results also suggest that other mechanisms likely contribute to outcome differences. We are not able to evaluate the potential role of chronic comorbidities, socioeconomic factors, or more detailed aspects of resuscitation or post-resuscitation care not captured by the Utstein elements. A better understanding of if and how these factors contribute to the outcome disparity may enable strategies to improve care.

Limitations

This study has limitations. As an observational study, relationships between exposures and outcomes are associations, and not necessarily causal. Unobserved confounding may contribute to associations, though we adjusted for known Utstein characteristics. Younger vs older age groups were centered around the average age of menopause as we were unable to measure blood hormone levels to confirm menopausal status. Thus, the age threshold for younger vs older patients was chosen as 55 years; we also performed sensitivity analyses according to age to account for variable onset of menopause effects, producing similar results. We evaluated several waveform measures to understand how this physiologic surrogate might explain differences in outcome. However, there may be other waveform measures that could better gauge physiologic status and might produce different results. The investigation is a single-site study of a high-performing EMS system which might affect generalizability; this characteristic, however, also means that variability in prehospital care is less likely to contribute as an unobserved confounder since outcome is strongly related to EMS system. Some eligible cases were not included given

missing or technical issues with the defibrillator recording, which may contribute some bias. These limitations should be considered in the context of this investigation's strengths. The study leverages a large, well-characterized cohort that incorporates VF waveform measures and Utstein predictors to evaluate outcome differences according to age and sex.

Conclusions

In this observational cohort study of VF-OHCA, we observed that women <55 years were more likely to achieve ROSC, survive, and survive with favorable neurological status compared to men <55 years; a sex-based outcome difference not observed among the older age group. A surrogate gauge of the heart's dynamic physiology – the VF waveform and specifically PSUR – mediated some of the outcome difference, though a complete explanation requires additional investigation to include other health domains.

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References

1. Myat A, Song KJ, Rea T. Out-of-hospital cardiac arrest: current concepts. Lancet. 2018 Mar 10;391(10124):970-979. doi: 10.1016/S0140-6736(18)30472-0. PMID: 29536861.
2. Berdowski J, Berg RA, Tijssen JG, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010 Nov;81(11):1479-87. doi: 10.1016/j.resuscitation.2010.08.006. Epub 2010 Sep 9. PMID: 20828914.
3. Virani SS, Alonso A, Benjamin EJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020 Mar 3;141(9):e139-e596. doi: 10.1161/CIR.0000000000000757. Epub 2020 Jan 29. PMID: 31992061.
4. Bhandari S, Doan J, Blackwood J, et al. Rhythm profiles and survival after out-of-hospital ventricular fibrillation cardiac arrest. *Resuscitation*. 2018;125:22-27. doi:10.1016/j.resuscitation.2018.01.037
5. Girotra S, Van Diepen S, Nallamothu BK, Carrel M, Vellano K, Anderson ML, et al. Regional variation in out-of-hospital cardiac arrest survival in the United States. Circulation. 2016;133(22):2159–68.
6. van Diepen S, Girotra S, Abella BS, Becker LB, Bobrow BJ, Chan PS, Fahrenbruch C, Granger CB, Jollis JG, McNally B, White L, Yannopoulos D, Rea TD. Multistate 5-Year Initiative to Improve Care for Out-of-Hospital Cardiac Arrest: Primary Results From the HeartRescue Project. J Am Heart Assoc. 2017;6(9). pii: e005716. doi: 10.1161/JAHA.117.005716. PMID: 28939711
7. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, Rea T, Lowe R, Brown T, Dreyer J, Davis D, Idris A, Stiell I; Resuscitation Outcomes Consortium Investigators. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008 Sep 24;300(12):1423-31. doi: 10.1001/jama.300.12.1423. Erratum in: JAMA. 2008 Oct 15;300(15):1763. PMID: 18812533.
8. Dumas F, Blackwood J, White L, Fahrenbruch C, Jouven X, Cariou A, Rea T. The relationship between chronic health conditions and outcome following out-of-hospital ventricular fibrillation cardiac arrest. Resuscitation. 2017;120:71-76. PMID: 28860011.
9. Chan PS, McNally B, Tang F, Kellermann A; CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation. 2014 Nov 18;130(21):1876-82. doi: 10.1161/CIRCULATIONAHA.114.009711. PMID: 25399396.
10. Oh SH, Park KN, Lim J, Choi SP, Oh JS, Cho IS, Lee BK, Kim YH, Kim YM, Kim HJ, Youn CS, Kim SH; Korean Hypothermia Network Investigators The impact of sex and age on neurological outcomes in out-of-hospital cardiac arrest patients with targeted temperature management. Crit Care. 2017 Nov 2;21(1):272. doi: 10.1186/s13054-017-1860-5. PMID: 29096675
11. Kim C, Fahrenbruch CE, Cobb LA, Eisenberg MS. Out-of-hospital cardiac arrest in men and women. Circulation. 2001;104(22):2699-703. PMID: 11723022
12. Johnson MA, Haukoos JS, Larabee TM, Daugherty S, Chan PS, McNally B, Sasson C. Females of childbearing age have a survival benefit after out-of-hospital cardiac arrest. Resuscitation. 2013 May;84(5):639-44. doi: 10.1016/j.resuscitation.2012.09.011. Epub 2012 Sep 15. PMID: 22986061.

13. Blewer AL, McGovern SK, Schmicker RH, May S, Morrison LJ, Aufderheide TP, Daya M, Idris AH, Callaway CW, Kudenchuk PJ, Vilke GM, Abella BS; Resuscitation Outcomes Consortium (ROC) Investigators. Gender Disparities Among Adult Recipients of Bystander Cardiopulmonary Resuscitation in the Public. Circ Cardiovasc Qual Outcomes. 2018 Aug;11(8):e004710. doi: 10.1161/CIRCOUTCOMES.118.004710. PMID: 30354377.
14. Blewer AL, Eng Hock Ong M. In pursuit of equity: Shedding light on gender differences in post-arrest care treatment of out-of-hospital cardiac arrest. Resuscitation. 2019 Oct;143:221-222. doi: 10.1016/j.resuscitation.2019.08.016. Epub 2019 Aug 14. PMID: 31421193.
15. Rea TD, Eisenberg MS, Becker LJ, Murray JA, Hearne T. Temporal trends in sudden cardiac arrest: a 25-year emergency medical services perspective. Circulation. 2003;107(22):2780-5. PMID: 12756155.
16. Neumar RW, Shuster M, Callaway CW, et al. Part 1: Executive Summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18 Suppl 2):S315-S367. doi:10.1161/CIR.0000000000000252. PMID: 26472989.
17. Perkins GD, Jacobs IG, Nadkarni VM, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation [published correction appears in Circulation. 2015 Sep 29;132(13):e168-9]. *Circulation*. 2015;132(13):1286-1300. doi:10.1161/CIR.0000000000000144
18. Wells DM, White LL, Fahrenbruch CE, Rea TD. Socioeconomic status and survival from ventricular fibrillation out-of-hospital cardiac arrest. Ann Epidemiol. 2016;26(6):418–423. PMID: 27174737
19. Rea TD, Eisenberg MS, Becker LJ, Murray JA, Hearne T. Temporal trends in sudden cardiac arrest: a 25-year emergency medical services perspective. Circulation. 2003;107(22):2780-5. PMID: 12756155.
20. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA. 2002;288(23):3008-13. PMID: 12479765.
21. Rea TD, Crouthamel M, Eisenberg MS, Becker LJ, Lima AR. Temporal patterns in long-term survival after resuscitation from out-of-hospital cardiac arrest. Circulation. 2003;108(10):1196-201. PMID: 12939219.
22. Kwok H, Prekker M, Grabinsky A, Carlbom D, Rea TD. Use of rapid sequence intubation predicts improved survival among patients intubated after out-of-hospital cardiac arrest. Resuscitation. 2013;84(10):1353-8.
23. Rea TD, Eisenberg MS, Becker LJ, Lima AR, Fahrenbruch CE, Copass MK, et al. Emergency medical services and mortality from heart disease: a community study. Annals of Emergency Medicine. 2003;41(4):494-9. PMID: 12658249.
24. Rea TD, Fahrenbruch C, Culley L, Donohoe RT, Hambly C, Innes J, Bloomingdale M, Subido C, Romines S, Eisenberg MS. CPR with chest compression alone or with rescue breathing. N Engl J Med. 2010;363(5):423-33. PMID: 20818863.

25. Nichol G, Leroux B, Wang H, Callaway CW, Sopko G, Weisfeldt M, Stiell I, Morrison LJ, Aufderheide TP, Cheskes S, Christenson J, Kudenchuk P, Vaillancourt C, Rea TD, Idris AH, Colella R, Isaacs M, Straight R, Stephens S, Richardson J, Condle J, Schmicker RH, Egan D, May S, Ornato JP; ROC Investigators. Trial of Continuous or Interrupted Chest Compressions during CPR. N Engl J Med. 2015 3;373(23):2203-14.
26. Aufderheide TP, Nichol G, Rea TD, Brown SP, Leroux BG, Pepe PE, Kudenchuk PJ, Christenson J, Daya MR, Dorian P, Callaway CW, Idris AH, Andrusiek D, Stephens SW, Hostler D, Davis DP, Dunford JV, Pirrallo RG, Stiell IG, Clement CM, Craig A, Van Ottingham L, Schmidt TA, Wang HE, Weisfeldt ML, Ornato JP, Sopko G; Resuscitation Outcomes Consortium (ROC) Investigators. A trial of an impedance threshold device in out-of-hospital cardiac arrest. N Engl J Med. 2011;365(9):798-806. PMID: 21879897.
27. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, Copass MK, Carlbom D, Deem S, Longstreth WT Jr, Olsufka M, Cobb LA. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2014;311(1):45-52.
28. Kudenchuk PJ, Brown SP, Daya M, Rea T, Nichol G, Morrison LJ, Leroux B, Vaillancourt C, Wittwer L, Callaway CW, Christenson J, Egan D, Ornato JP, Weisfeldt ML, Stiell IG, Idris AH, Aufderheide TP, Dunford JV, Colella MR, Vilke GM, Brienza AM, Desvigne-Nickens P, Gray PC, Gray R, Seals N, Straight R, Dorian P; Resuscitation Outcomes Consortium Investigators. Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest. N Engl J Med. 2016;374(18):1711-22. PMID: 27043165.
29. Schoene P, Coult J, Murphy L, Fahrenbruch C, Blackwood J, Kudenchuk P, Sherman L, Rea T. Course of quantitative ventricular fibrillation waveform measure and outcome following out-of-hospital cardiac arrest. Heart Rhythm. 2014;11(2):230-6. PMID: 24177369
30. Coult J, Blackwood J, Sherman L, Rea TD, Kudenchuk PJ, Kwok H Ventricular Fibrillation Waveform Analysis During Chest Compressions to Predict Survival From Cardiac Arrest. Circ Arrhythm Electrophysiol. 2019; 12(1): PMID: 30626208
31. Rea TD, Helbock M, Perry S, Garcia M, Cloyd D, Becker L, Eisenberg M.. Increasing use of cardiopulmonary resuscitation during out-of-hospital ventricular fibrillation arrest: survival implications of guideline changes. Circulation. 2006;114(25):2760-5 9. PMID: 17159062
32. Cheskes S, Schmicker RH, Christenson J, Salcido DD, Rea T, Powell J, Edelson DP, Sell R, May S, Menegazzi JJ, Van Ottingham L, Olsufka M, Pennington S, Simonini J, Berg RA, Stiell I, Idris A, Bigham B, Morrison L; Resuscitation Outcomes Consortium (ROC) Investigators.. Perishock pause: an independent predictor of survival from out-of-hospital shockable cardiac arrest. Circulation. 2011;124(1):58-66. PMID:21690495
33. Christenson J, Andrusiek D, Everson-Stewart S, Kudenchuk P, Hostler D, Powell J, Callaway CW, Bishop D, Vaillancourt C, Davis D, Aufderheide TP, Idris A, Stouffer JA, Stiell I, Berg R; Resuscitation Outcomes Consortium Investigators. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation. 2009;120(13):1241-7. PMID: 19752324
34. Kudenchuk PJ, Redshaw JD, Stubbs BA, Fahrenbruch CE, Dumas F, Phelps R, Blackwood J, Rea TD, Eisenberg MS. Impact of changes in resuscitation practice on survival resulting from nonshockable arrhythmias. Circulation. 2012;125(14):1787-94. PMID: 22474256

35. Bhandari S, Doan J, Blackwood J, Coult J, Kudenchuk P, Sherman L, Rea T, Kwok H. Rhythm profiles and survival after out-of-hospital ventricular fibrillation cardiac arrest. Resuscitation. 2018 Apr;125:22-27.
36. Kwok H, Coult J, Liu C, Blackwood J, Kudenchuk PJ, Rea TD, Sherman LS. An Accurate Method for Real-time Chest Compression Detection from the Impedance Signal. Resuscitation. 2016.:22-28.
37. Kwok H, Coult J, Drton M, Rea TD, Sherman L. Adaptive Rhythm Sequencing: A Method for Dynamic Rhythm Classification during CPR. *Resuscitation*. 2015; 91: 26-31. PMID: 25805433
38. Coult J, Kwok H, Sherman L, Blackwood J, Kudenchuk PJ, Rea TD. Ventricular fibrillation waveform measures combined with prior shock outcome predict defibrillation success during cardiopulmonary resuscitation. J Electrocardiol. 2018;51(1):99-106. PMID: 28893389
39. Hidano D, Coult J, Blackwood J, Fahrenbruch C, Kwok H, Kudenchuk P, Rea T. Ventricular fibrillation waveform measures and the etiology of cardiac arrest. Resuscitation. 2016;109:71-75. PMID: 27784613
40. Hostler D, Everson-Stewart S, Rea TD, Stiell IG, Callaway CW, Kudenchuk PJ, Sears GK, Emerson SS, Nichol G; Resuscitation Outcomes Consortium Investigators. Effect of real-time feedback during cardiopulmonary resuscitation outside hospital: prospective, cluster-randomised trial. BMJ. 2011;342:d512. PMID: 21296838
41. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. Statistics in medicine 1997;16(13):1515-27. PMID: 9249922
42. Dumas F, Coult J, Blackwood J, Kudenchuk P, Cariou A, Rea TD. The association of chronic health status and survival following ventricular fibrillation cardiac arrest: Investigation of a primary myocardial mechanism. Resuscitation. 2019 Apr;137:190-196. doi: 10.1016/j.resuscitation.2019.02.018. Epub 2019 Feb 19. PMID: 30794830.
43. Starks MA, Schmicker RH, Peterson ED, May S, Buick JE, Kudenchuk PJ, Drennan IR, Herren H, Jasti J, Sayre M, Stub D, Vilke GM, Stephens SW, Chang AM, Nuttall J, Nichol G; Resuscitation Outcomes Consortium (ROC). Association of Neighborhood Demographics With Out-of-Hospital Cardiac Arrest Treatment and Outcomes: Where You Live May Matter. JAMA Cardiol. 2017;2(10):1110-1118.
44. Rea TD, Cook AJ, Stiell IG, Powell J, Bigham B, Callaway CW, Callaway CW, Chugh S, Aufderheide TP, Morrison L, Terndrup TE, Beaudoin T, Wittwer L, Davis D, Idris A, Nichol G; Resuscitation Outcomes Consortium Investigators.. Predicting Survival After Out-of-Hospital Cardiac Arrest: Role of the Utstein Data Elements. Ann Emerg Med. 2010;55(3):249–57. PMID: 19944488
45. Imai, K., L. Keele, and D. Tingley (2010a): "A general approach to causal media-tion analysis."Psychological Methods, 15, 309–334.
46. Imai, K., L. Keele, and T. Yamamoto (2010b): "Identification, Inference and Sen-sitivity Analysis for Causal Mediation Effects,"Statistical Science, 25, 51–71.

Table 1. Patient characteristics according age and sex group.

	Overall	Male < 55	Female < 55	Male 55+	Female 55+
n	1526	343	120	843	220
Patient characteristics					
Age, median [IQR] (years)	62 [52, 72]	48 [41, 51]	45 [38, 51]	67 [61, 75]	72 [63, 78]
Cardiac Etiology, n (%)	1398 (91.6)	296 (86.3)	94 (78.3)	804 (95.4)	204 (92.7)
Public Location, n (%)	487 (31.9)	138 (40.2)	34 (28.3)	259 (30.7)	56 (25.5)
Resuscitation process					
EMS Response Time, min, median [IQR]	5.3 [4.2, 6.6]	5.4 [4.0, 6.6]	5.2 [4.0, 6.3]	5.3 [4.3, 6.8]	5.2 [4.3, 6.1]
Bystander CPR, n (%)	1153 (75.6)	251 (73.2)	96 (80.0)	646 (76.6)	160 (72.7)
Witnessed Arrest Categories, n (%)					
Unwitnessed	333 (21.8)	67 (19.5)	30 (25.0)	186 (22.1)	50 (22.7)
Witnessed by EMS	69 (4.5)	24 (7.0)	7 (5.8)	24 (2.8)	14 (6.4)
Witnessed by other	1124 (73.7)	252 (73.5)	83 (69.2)	633 (75.1)	156 (70.9)
VF waveform measures, median [IQR]					
FREQ, Hz	4.58 [3.11, 6.16]	4.52 [3.17, 6.26]	5.49 [3.27, 7.26]	4.39 [2.99, 5.92]	4.97 [3.52, 6.42]
PEAK, mV	0.76 [0.53, 1.03]	0.78 [0.53, 1.10]	0.87 [0.61, 1.16]	0.73 [0.50, 0.99]	0.78 [0.59, 0.99]
PSUR	0.29 [0.22, 0.56]	0.30 [0.23, 0.55]	0.48 [0.24, 0.70]	0.26 [0.22, 0.52]	0.32 [0.23, 0.61]
AMSA, mV-Hz	9.53 [5.90, 13.27]	9.95 [6.31, 13.97]	10.97 [7.11, 17.08]	9.07 [5.60, 12.62]	9.63 [6.64, 13.25]
Post-arrest Care, n (%)					
Targeted Temperature Management*	589 (48.9)	120 (45.3)	49 (46.2)	338 (52.0)	82 (44.6)
Angiography*	759 (63.0)	194 (73.2)	59 (55.7)	408 (62.8)	98 (53.3)
Clinical Outcomes					
Survival to hospital discharge, n (%)	695 (45.5)	186 (54.2)	80 (66.7)	333 (39.5)	96 (43.6)
Favorable neurological survival, n (%)	648 (42.5)	174 (50.7)	73 (60.8)	315 (37.4)	86 (39.1)
Sustained ROSC, n (%)	1094 (71.7)	242 (70.6)	98 (81.7)	585 (69.4)	169 (76.8)

Abbreviations: EMS = Emergency Medical Services; CPR = cardiopulmonary resuscitation; VF = Ventricular Fibrillation; ECG = Electrocardiogram; PEAK = Median Peak Amplitude; FREQ = Peak Frequency; PSUR = Probability of Survival; AMSA = Amplitude Spectral Area; ROSC = return of spontaneous circulation.

Table 2. Odds ratios for variable association with outcomes, adjusted and unadjusted, OR (95% CI).

	Variable		Unadjusted	Utstein Adjusted	Mediation Models: AMSA	FREQ	PEAK	PSUR
Outcome = Hospital Survival	Public Location		1.61 (1.30-2.00)	1.44 (1.15-1.82)	1.28 (1.00-1.63)	1.31 (1.03-1.67)	1.39 (1.10-1.76)	1.21 (0.94-1.55)
	Time to First Responder Arrival (min)		0.88 (0.84-0.92)	0.90 (0.85-0.95)	0.91 (0.86-0.96)	0.92 (0.87-0.97)	0.91 (0.86-0.95)	0.90 (0.86-0.96)
	Cardiac Etiology		1.87 (1.28-2.77)	2.26 (1.49-3.46)	2.34 (1.50-3.71)	2.05 (1.32-3.23)	2.49 (1.62-3.87)	1.94 (1.25-3.06)
	Bystander CPR		1.14 (0.90-1.44)	1.53 (1.17-2.01)	1.16 (0.87-1.56)	1.20 (0.91-1.61)	1.36 (1.03-1.80)	1.12 (0.84-1.51)
	Witnessed Status	Witnessed by EMS	4.98 (2.88-8.83)	5.22 (2.83-9.86)	2.90 (1.53-5.64)	3.37 (1.77-6.56)	3.77 (2.01-7.23)	3.19 (1.64-6.29)
		Witnessed by other	2.22 (1.71-2.89)	2.21 (1.69-2.91)	1.79 (1.34-2.39)	1.84 (1.38-2.46)	1.97 (1.49-2.61)	1.77 (1.33-2.38)
	Age-Sex Group	Female <55	1.69 (1.10-2.63)	1.93 (1.23-3.09)	1.76 (1.08-2.90)	1.85 (1.13-3.07)	1.81 (1.13-2.93)	1.54 (0.94-2.56)
		Male ≥55	0.55 (0.43-0.71)	0.53 (0.40-0.69)	0.53 (0.40-0.70)	0.53 (0.40-0.71)	0.52 (0.40-0.69)	0.52 (0.39-0.70)
		Female ≥55	0.65 (0.46-0.92)	0.62 (0.44-0.89)	0.58 (0.40-0.85)	0.54 (0.37-0.78)	0.60 (0.41-0.86)	0.51 (0.35-0.75)
	Waveform Measures	AMSA	2.45 (2.16-2.79)	-	2.26 (1.98-2.59)	-	-	-
		FREQ	2.38 (2.10-2.71)	-	-	2.21 (1.94-2.53)	-	-
		PEAK	1.77 (1.58-1.99)	-	-	-	1.66 (1.47-1.87)	-
		PSUR	2.52 (2.25-2.84)	-	-	-	-	2.36 (2.09-2.67)
Outcome = Favorable Neurologic Survival	Public Location		1.72 (1.38-2.14)	1.55 (1.23-1.95)	1.38 (1.08-1.76)	1.41 (1.11-1.80)	1.49 (1.18-1.89)	1.30 (1.01-1.67)
	Time to First Responder Arrival (min)		0.88 (0.83-0.92)	0.90 (0.85-0.94)	0.90 (0.86-0.96)	0.92 (0.87-0.97)	0.90 (0.86-0.95)	0.90 (0.85-0.95)
	Cardiac Etiology		1.91 (1.30-2.87)	2.21 (1.45-3.42)	2.30 (1.47-3.68)	2.01 (1.28-3.20)	2.42 (1.57-3.79)	1.88 (1.20-3.00)
	Bystander CPR		1.13 (0.89-1.43)	1.57 (1.19-2.07)	1.20 (0.89-1.61)	1.22 (0.91-1.64)	1.41 (1.06-1.87)	1.14 (0.85-1.53)
	Witnessed Status	Witnessed by EMS	5.40 (3.13-9.55)	5.81 (3.14-10.97)	3.28 (1.73-6.36)	3.75 (1.97-7.29)	4.28 (2.28-8.18)	3.53 (1.82-6.97)
		Witnessed by other	2.26 (1.73-2.97)	2.23 (1.69-2.96)	1.80 (1.34-2.43)	1.85 (1.38-2.49)	2.00 (1.50-2.66)	1.77 (1.32-2.40)
	Age-Sex Group	Female <55	1.51 (0.99-2.31)	1.72 (1.10-2.71)	1.52 (0.94-2.47)	1.58 (0.97-2.60)	1.60 (1.01-2.55)	1.32 (0.81-2.17)
		Male ≥55	0.58 (0.45-0.75)	0.56 (0.43-0.74)	0.57 (0.43-0.76)	0.57 (0.43-0.76)	0.56 (0.43-0.74)	0.56 (0.42-0.75)
		Female ≥55	0.62 (0.44-0.88)	0.60 (0.42-0.86)	0.56 (0.38-0.81)	0.51 (0.35-0.75)	0.57 (0.40-0.83)	0.48 (0.33-0.72)
	Waveform Measures	AMSA	2.46 (2.16-2.81)	-	2.26 (1.98-2.60)	-	-	-
		FREQ	2.47 (2.17-2.82)	-	-	2.29 (2.00-2.63)	-	-
		PEAK	1.73 (1.54-1.94)	-	-	-	1.61 (1.43-1.82)	-
		PSUR	2.57 (2.29-2.89)	-	-	-	-	2.41 (2.13-2.73)
Outcome = Sustained ROSC	Public Location		1.23 (0.97-1.58)	1.19 (0.93-1.54)	1.05 (0.81-1.37)	1.09 (0.84-1.41)	1.14 (0.88-1.48)	1.02 (0.78-1.33)
	Time to First Responder Arrival (min)		0.94 (0.89-0.98)	0.95 (0.90-0.99)	0.96 (0.91-1.00)	0.97 (0.92-1.00)	0.96 (0.91-1.00)	0.96 (0.91-0.99)
	Cardiac Etiology		1.64 (1.12-2.38)	1.70 (1.14-2.51)	1.64 (1.08-2.47)	1.53 (1.01-2.29)	1.80 (1.19-2.70)	1.47 (0.97-2.20)
	Bystander CPR		1.30 (1.01-1.67)	1.51 (1.15-1.99)	1.19 (0.89-1.58)	1.31 (0.98-1.73)	1.32 (0.99-1.75)	1.21 (0.91-1.60)
	Witnessed Status	Witnessed by EMS	2.36 (1.29-4.57)	2.70 (1.41-5.45)	1.53 (0.78-3.16)	1.93 (0.99-3.96)	1.82 (0.93-3.74)	1.74 (0.88-3.61)
		Witnessed by other	1.70 (1.31-2.21)	1.68 (1.28-2.18,)	1.35 (1.02-1.78)	1.44 (1.09-1.89)	1.43 (1.08-1.88)	1.38 (1.05-1.82)
	Age-Sex Group	Female <55	1.86 (1.13-3.18)	1.96 (1.17-3.39)	1.84 (1.08-3.27)	1.92 (1.13-3.38)	1.84 (1.08-3.23)	1.64 (0.96-2.91)
		Male ≥55	0.95 (0.72-1.24)	0.91 (0.68-1.21)	0.98 (0.73-1.32)	0.96 (0.72-1.29)	0.94 (0.70-1.26)	0.97 (0.72-1.31)
		Female ≥55	1.38 (0.94-2.05)	1.35 (0.91-2.03)	1.36 (0.90-2.07)	1.32 (0.88-2.00)	1.33 (0.89-2.02)	1.27 (0.84-1.94)
	Waveform Measures	AMSA	2.03 (1.80-2.31)	-	1.92 (1.69-2.18)	-	-	-
		FREQ	1.77 (1.58-1.99)	-	-	1.66 (1.47-1.87)	-	-
		PEAK	1.79 (1.59-2.02)	-	-	-	1.68 (1.49-1.91)	-
		PSUR	2.20 (1.92-2.53)	-	-	-	-	2.07 (1.80-2.39)

Utstein adjusted model includes adjustment by Public Location, Time to First Responder Arrival, Cardiac Etiology, bystander CPR, Witnessed Status, and Age-Sex Group. Referent group for witnessed status is Unwitnessed group, and referent group for Age-Sex Group is Male <55. Each Mediation Model includes the Utstein adjusted model and the waveform measure.

Abbreviations: CPR = cardiopulmonary resuscitation; VF = Ventricular Fibrillation; PEAK = Median Peak Amplitude; FREQ = Peak Frequency; PSUR = Probability of Survival; AMSA = Amplitude Spectral Area; ROSC = return of spontaneous circulation.

Table 3. Causal mediation analysis.

Comparison	Outcome	Parameter	VF waveform measures as mediators			
			FREQ	PEAK	PSUR	AMSA
Women < 55 vs Men < 55	Survival	VF-waveform mediated effect	0.024	0.022	0.059	0.031
		Non-waveform mediated effect	0.101	0.106	0.066	0.093
		Proportion Mediated	0.191	0.172	0.470	0.250
Women < 55 vs Men < 55	Favorable Neurologic Survival (CPC1-2)	VF-waveform mediated effect	0.027	0.021	0.063	0.031
		Non-waveform mediated effect	0.078	0.087	0.040	0.071
		Proportion Mediated	0.256	0.192	0.610	0.306
Women < 55 vs Men < 55	Sustained ROSC	VF-waveform mediated effect	0.017	0.018	0.047	0.023
		Non-waveform mediated effect	0.093	0.089	0.061	0.088
		Proportion Mediated	0.156	0.165	0.431	0.203

Effect sizes are expressed as absolute differences in outcomes.

Abbreviations: CPC1-2 = Cerebral Performance Category 1-2 ROSC = return of spontaneous circulation; VF = Ventricular Fibrillation; PEAK = Median Peak Amplitude; FREQ = Peak Frequency; PSUR = Probability of Survival; AMSA = Amplitude Spectral Area; ROSC = return of spontaneous circulation.