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Systematic review of the relationship between comorbidity and out-of-hospital cardiac arrest outcomes

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ABSTRACT

Objectives To assess the current evidence on the effect pre-arrest comorbidity has on survival and neurological outcomes following out-of-hospital cardiac arrest (OHCA).

Design Systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data sources MEDLINE, Ovid Embase, Scopus, CINAHL, Cochrane Library and MedNar were searched from inception to 31 December 2018.

Eligibility criteria Studies included if they examined the association between prearrest comorbidity and OHCA survival and neurological outcomes in adult or paediatric populations.

Data extraction and synthesis Data were extracted from individual studies but not pooled due to heterogeneity. Quality of included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.

Results This review included 29 observational studies. There were high levels of clinical heterogeneity between studies with regards to patient recruitment, inclusion criteria, outcome measures and statistical methods used which ultimately resulted in a high risk of bias. Comorbidities reported across the studies were diverse, with some studies reporting individual comorbidities while others reported comorbidity burden using tools like the Charlson Comorbidity Index. Generally, prearrest comorbidity was associated with both reduced survival and poorer neurological outcomes following OHCA with 79% (74/94) of all reported adjusted results across 23 studies showing effect estimates suggesting lower survival with 42% (40/94) of these being statistically significant. OHCA survival was particularly reduced in patients with a prior history of diabetes (four out of six studies). However, a prearrest history of myocardial infarction appeared to be associated with increased survival in one of four studies.

Conclusions Prearrest comorbidity is generally associated with unfavourable OHCA outcomes, however differences between individual studies makes comparisons difficult. Due to the clinical and statistical heterogeneity across the studies, no meta-analysis was conducted. Future studies should follow a more standardised approach to investigating the impact of comorbidity on OHCA outcomes.

PROSPERO registration number CRD42018087578

Strengths and limitations of this study

- ► To the best of our knowledge, this is the first systematic review examining the relationship between prearrest comorbidity and out-of-hospital cardiac arrest (OHCA) outcomes (survival or neurological).
- ► This study identifies the limitations of current research in the area of prearrest comorbidity and OHCA outcomes, and provides direction for future research.
- ► Significant clinical heterogeneity between studies prevented a meta-analysis.

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a sudden and commonly fatal medical emergency.[1 2] Although a number of patient-specific and arrest-specific factors have been identified that influence patient survival,[3 4] these factors fail to fully explain the variability in outcomes.[5 6] The effect of prearrest comorbidity on outcomes in patients with OHCA is poorly understood.[7]

It has been suggested that a better understanding of the effect that comorbidity has on OHCA outcomes could lead to a number of benefits such as: improved understanding of the epidemiology of cardiac arrest,[8] more informed end-of-life planning,[9 10] improved public health policies to preemptively manage 'at risk' populations[8 11] and improved prognostication.[3 7 9 12] A number of authors have investigated the association between prearrest comorbidity and OHCA survival with some reporting comorbidity to be negatively associated with survival,[6 13] while others reporting no relationship.[14] Regarding neurological outcomes, similar variability in findings has been observed, with some authors reporting a negative relationship[15] and others reporting no relationship.[10 12] However, despite the variability in findings and continued interest in the topic, no systematic review examining the association of prearrest comorbidity and OHCA outcome has been conducted to date. This systematic review provides an overview of the current evidence regarding the association between prearrest comorbidity and

patient survival and neurological outcomes following OHCA.

METHODS

Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[16] was followed in this systematic review.

Review question

In patients with OHCA, do preexisting chronic health conditions result in poorer survival to hospital discharge and neurological outcomes?

Eligibility criteria

To be eligible for inclusion in this systematic review, studies had to include: (1) cases of OHCA of medical aetiology[17] and (2) quantitative comparison between comorbidity and OHCA outcome (either survival or neurological outcome). Survival outcome could include survival to hospital discharge or 30-day survival, both being survival metrics recommended by the Utstein report.[17] No restrictions were placed on the tool used to measure comorbidity or neurological outcome, and both adult and paediatric cases were included. No publication date or language restrictions were applied. There were no ethical requirements for inclusion in this systematic review.

All comparative study types were considered for inclusion except: (1) editorials, case studies/case reports/case series, commentaries, conference abstracts, opinion pieces and letters; (2) in-hospital cardiac arrests or arrests that occurred during interhospital transfer; (3) cardiac arrests with a primary aetiology of trauma, drug-related, drowning, electrocution or asphyxia as defined by the 2015 Utstein OHCA reporting guidelines.[17]

Data on individual cancer sub-types were excluded as this level of detail was beyond the scope of this review. Data on prior surgeries, medication use or conditions that are congenital, idiopathic, of short duration and/or unlikely to have long term implications were not considered to constitute a comorbidity for this review.

Data sources

The databases Ovid MEDLINE, Ovid Embase, Scopus, CINAHL and Cochrane Library were searched for all eligible studies from inception to 31 December 2018. The search engine MedNar was searched until 31 December 2018 for grey literature. Reference lists from all relevant studies were searched to identify any additional studies.

Patient and public involvement

No patient or public were involved in the design or planning of this study.

Search strategy

Search terms were grouped into two broad categories of 'OHCA' and 'comorbidity' and combined using the Boolean operator 'AND'. The search strategies for each of the databases have been provided in online supplementary appendix 1.

Study selections

Titles and abstracts were initially screened by a single author (DM) to identify potentially relevant papers. Full-text review was then performed by two authors (DM and SB) independently to identify studies that met the eligibility criteria, with disagreements resolved by a third reviewer (JF). As a subsequent check to ensure a high level of sensitivity, JF rescreened all titles and abstracts. Any papers identified from this second screen then underwent full-text review by two authors (DM and SB) and were included if they met eligibility criteria (by mutual agreement of DM and SB).

Data collection

Data were extracted by DM from the relevant studies and entered into an Excel spreadsheet. Data extracted included information on authors, title, publication year, study location, study period, aims, study design, comorbidity, type of comorbidity measurement, patient survival and/or neurological outcome. Additionally, prehospital resuscitation factors (eg, witness status and bystander cardiopulmonary resuscitation) were extracted where available. Where a study provided relevant outcomes graphically (eg, in a forest plot) but did not provide corresponding effect estimates, the authors of those studies were contacted for additional data.

Risk of bias in individual studies

Risk of bias of individual studies was independently assessed by two authors (DM and SB) using the Newcastle-Ottawa Quality Assessment Scale for cohort studies, and any disagreements were resolved by mutual consensus.

Summary measures

We planned to use ORs to compare survival or neurological outcomes between cases with and without comorbidities. In studies that did not provide ORs, crude ORs were calculated wherever possible. Studies that provided mortality OR were converted to survival OR by calculating the reciprocal of the mortality OR for both unadjusted and adjusted values. Studies that provided statistics other than OR (eg, hazard ratios) were not included in forest plots. Where cerebral performance categories (CPC)[18] were reported, we used CPC of 1 or 2 as an indicator of good neurological outcome. ORs for survival to hospital discharge and 30-day survival were considered equivalent and grouped together. For both survival and neurological outcomes, results were included in a forest plot only if two or more studies reported ORs on the same comorbidity. RevMan V.5.3 was used to obtain relevant figures such as forest plots.[19] Where individual studies provided different descriptors for the same or similar comorbidity, we planned to group these where appropriate (eg, hyperlipidaemia and hypercholesterolaemia). Any results exclusively associated with an initial non-shockable cardiac

arrest rhythm were excluded. Where multiple results were reported by a single study for the same exposure but for varying subgroup (for example by initial cardiac arrest rhythm), only one set of results were utilised to prevent duplication. Given the well documented prognostic influence of specific other covariates on OHCA outcomes,[4 20 21] adjusted results were preferentially used.

RESULTS

Study selection

The initial search identified 6395 citations. After removal of duplicates 3132 remained. A total of 75 potential studies were identified after title and abstract screening against inclusion/exclusion criteria. After full-text review, 29 studies were included. These results are summarised in the PRISMA flow diagram (figure 1). Of the 46 excluded studies, 24 were excluded because they did not directly document a comparison between OHCA outcome and at least one comorbid condition or did not allow for the direct calculation of such a relationship. Our search also identified two studies[22 23] that conducted relevant analysis however did not report these results and were therefore excluded from this review. Our initial article search identified three papers from Taiwan[24–26] with significant cohort overlap. To avoid duplication of results only the paper[26] with the most comprehensive analysis of comorbidity was included within this review. Similarly, of two papers from Australia[9 27] with significant cohort overlap, only one paper[9] was included in the review.

Study characteristics

A summary of all included studies is provided in tables 1 and 2. Studies presented in table 1 (n=21) directly investigated the effect of comorbidity on OHCA outcome, while those in table 2 (n=8) had alternative primary aims but still provided information on the association between comorbidity and OHCA outcomes. Results from each of the individual studies are shown online supplementary table 1 (for survival to hospital discharge outcomes) and online supplementary table 2 (for neurological outcomes). There were 18 studies conducted in Europe,[3 5 10 13 15 28–40] four in the USA,[8 12 41 42] three in Asia,[20 26 43] two multinational studies,[11 14] one in Australia[9] and one in Canada.[44] The number of patients enrolled in each study varied from n=63[30] to n=2 47 684.[41] Patient inclusion age varied between studies, with 19 studies restricted to adults (≥16 years),[3 8 9 12 20 26 28 29 31 33 36–44] one[10] restricted to 70 years or over, seven placing no age restrictions[5 11 13 15 32 34 35] and two studies being unclear about age.[14 30] Cohort recruitment points varied greatly also, with 15 studies using scene of arrest as the enrolment point,[5 8–11 13 20 31–33 38–40 42 44] 6 using emergency department (ED) admission[12 15 26 35–37] and 8 using hospital admission.[3 14 28–30 34 41 43] Cardiac arrest aetiology was identified as either cardiac or non-traumatic in 12 studies,[5 8–12 20 26 31 33 36 41] while the remaining studies either placed no restriction or were unclear. Patient clinical inclusion characteristics were highly variable between the studies. Eight studies placed no restrictions[9–11 20 26 31 40 44] on inclusion criteria while 21 studies restricted inclusion to patients with one or more clinical characteristics. These clinical characteristics included such factors as initial presenting cardiac rhythm,[5 8 32 34 42] whether the arrest was witnessed,[33 38] Glasgow Coma Scale score after successful resuscitation,[3 28 29] presence of a particular medical condition and/or admittance to a specific hospital department[12 14 15 30 35–37 41 43] and/or certain procedures or treatments received (eg, hypothermia; coronary angiograph).[3 28 43]

A number of studies had overlapping cohorts (overlapping geographical regions and recruitment dates). This included two studies from the Netherlands[5 10] and two from Sweden.[13 34] However, all four studies were included in this review as they differed sufficiently in inclusion criteria, study aims or recruitment period. Four studies from Denmark[29 37 39 40] had overlapping cohorts but generally examined different outcomes. Where the same or similar outcomes were examined, results from only one of the studies was used in this review. A fifth Danish study[3] was also included as the cohort overlap with the other four Danish studies was minimal. Three included US studies[8 12 42] have a possible cohort overlap, with a fourth study[41] that sourced its cohort from a nationwide inpatient sample. However, this overlap would be 20% at most and therefore it was decided to include all four studies.

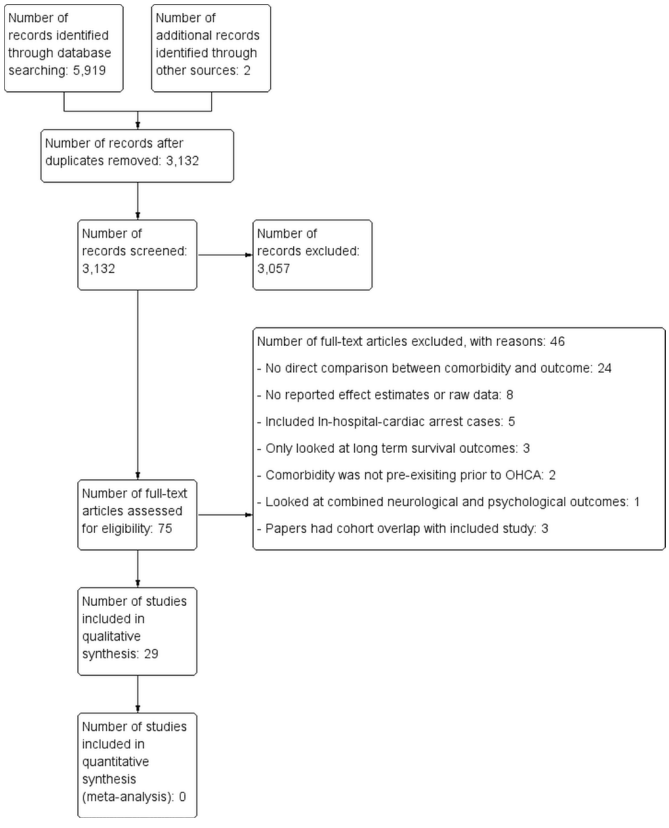

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies. OHCA, out-of-hospital cardiac arrest.

Table 1 Characteristics of included studies that directly investigated the influence of comorbidity on OHCA outcomes

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Andrew *et al* 2017[9]	Australia	Retrospective cohort	15953	Jan 2007–Dec 2014	Survival to hospital discharge	CCI=0,1,2,3,≥4, hypertension, diabetes, myocardial infarction, cerebrovascular disease, congestive heart failure, chronic obstructive disease, cancer, metastatic cancer, dementia, peripheral vascular disease, peptic ulcer, HIV/AIDS, skin ulcers, connective tissue disease.	Ambulance patient care records.	All non-traumatic arrests with an attempted resuscitation.	≥16
Beesems *et al* 2015[10]	Netherlands	Prospective cohort	851	Jan 2009–Dec 2011	Survival with good neurological outcome (CPC 1–2)	CCI ≥4.	Patients general practitioner.	All non-traumatic arrest patients without DNR orders and in whom resuscitation was started.	≥70
Blom *et al* 2013[5]	Netherlands	Prospective cohort	1172	2005–2008	30-day survival Neurological outcome at hospital discharge	Cardiovascular disease, obstructive pulmonary disease.	Presence of at least two condition-specific pharmacy prescriptions.	All VF/VT OHCA of presumed cardiac aetiology in whom resuscitation was attempted.	Any
Carew *et al* 2007[42]	USA	Retrospective cohort	1043	Jan 1999– Dec 2003	Survival to hospital discharge	Number of chronic conditions.	Ambulance patient care records.	All VF cardiac arrest patients who had an arrest of presumed cardiac aetiology/heart disease.	≥18
Corrada *et al* 2013[30]	Italy	Prospective cohort	63	2004–2009	Neurological outcome at discharge	Heart disease.	Unclear.	OHCA patients admitted to cardiac intensive care unit alive.	Unclear
de Vreede-Swagemakers *et al* 1998[31]	Netherlands	Prospective cohort	288	Jan 1991–Dec 1995	Survival to hospital discharge	Cardiac history.	Patients general practitioner.	All OHCA where CPR was attempted by EMS and arrest was not due to trauma or intoxication or patient in terminal stage of disease.	20–75
Dickey and Adgey 1992[32]	Northern Ireland (UK)	Prospective cohort	281	Jan 1966–Dec 1987	In-hospital mortality	Cerebrovascular accident, myocardial infarction.	Unclear.	All OHCA patients with an initial rhythm of VF.	Any

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Dumas *et al* 2017[8]	USA	Prospective cohort	1166	Jan 2007– Dec 2013	Survival to hospital discharge, neurological outcome at discharge (CPC)	CCI=0,1,2,3, atrial fibrillation, cancer, cerebrovascular accident, congestive cardiac failure, coronary artery disease, diabetes, gastrointestinal disease, heart disease, HIV, hypercholesterolaemia, hypertension, kidney disease, liver disease, lung disease, mental health, metabolic disease, myocardial infarction, non-cardiac history, non-neurological history, peripheral artery disease, prior cardiac arrest, tissue/ inflammatory disease, valvulopathy.	Ambulance patient care records.	Non-traumatic OHCA with initial rhythm of VF.	≥18
Herlitz *et al* 1995[34]	Sweden	Prospective cohort	488	1981–1992	In-hospital mortality	Myocardial infarction, angina pectoris, hypertension, diabetes, congestive heart failure, cerebrovascular disease, asthma.	Unclear.	All OHCA patients with initial rhythm of VF who were hospitalised alive.	Any
Hirlekar *et al* 2018[38]	Sweden	Retrospective cohort	12012	2011–2015	30-day survival	CCI=0–2, 3–4, 5–6,>6, cancer, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disorder/ rheumatic, dementia, diabetes, diabetes (with complications), liver disease (mild), myocardial infarction, paraplegia/hemiplegia, peptic ulcer disease, peripheral vascular disease, renal disease.	National Patient Registry.	All bystander-witnessed patients with OHCA.	≥18

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Iqbal *et al* 2015[15]	UK	Prospective cohort	174	2011–2013	Neurological outcome (modified Rankin Scale, mRS) at discharge	CCI.	National Institute for Cardiovascular Outcomes Research database.	All OHCA patients who were brought to emergency department with ROSC.	Any
Kang *et al* 2017[20]	South Korea	Retrospective cohort	341	Jan 2009 – Dec 2014	Survival to hospital discharge, neurological outcome (CPC)	Cancer.	Electronic medical records.	All non-traumatic OHCA. Cases of hanging, intoxication and drowning were excluded.	≥18
Larsson *et al* 2005[13]	Sweden	Prospective cohort	1377	Oct 1980–Oct 2003	Survival to hospital discharge	Angina pectoris, diabetes, myocardial infarction.	Hospital records and general practitioner.	All OHCA in whom resuscitation was attempted and patients were admitted to hospital alive.	Any
Lee *et al* 2018[11]	Japan, Singapre, South Korea, Malaysia, Taiwan, Thailand UAE	Retrospective cohort	19044	2009–2012	Survival to hospital discharge, neurological outcome at discharge (CPC)	1, 2 or three conditions, heart disease	Hospital records, ambulance reports and ambulance dispatch records.	All non-traumatic OHCA where resuscitation was commenced and where patient's medical history was known.	Any
Parry *et al* 2017[44]	Canada	Retrospective cohort	10097	2012–2014	Survival to hospital discharge, neurological outcome (mRS)	Diabetes	In-hospital records.	All OHCA's treated by ambulance services that had data on diabetes status.	≥18
Roedl *et al* 2017[35]	Austria	Prospective cohort	1068	Jan 2005–Jan 2012	6-month neurological outcome (CPC)	CCI=1,≥4, liver cirrhosis.	Hospital screening.	All OHCA patients admitted to the emergency department after ROSC.	Any

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Salam *et al* 2018[3]	Denmark	Prospective cohort	666	Jun 2002–2011	30-day mortality	CCI ≥1, cancer, cancer (metastatic), cerebrovascular disease, congestive heart failure, chronic kidney disease, connective tissue disease, coronary disease, dementia, diabetes, diabetes (with complications), gastric/duodenal ulcer, hemiplegia, hypercholesterolaemia, hypertension, liver disease, malignant haematological disease, acute myocardial infarction, peripheral artery disease, psychiatric disorder, pulmonary disease.	National patient registry and chart review.	Comatosed patients (GCS<8), who were successfully resuscitated from OHCA, admitted and treated with TTM (32–36 C) for 24 hours.	≥18
Søholm *et al* 2015[40]	Denmark	Retrospective cohort	2527	2007–2011	Survival to hospital discharge	CCI 1, 2,≥3, cancer, cancer (metastatic), cerebrovascular disease, congestive heart failure, diabetes, diabetes (with complications), hemiplegia, ischaemic heart disease, liver disease (mild), moderate/severe liver disease, moderate/severe renal disease, peptic ulcer, peripheral vascular disease, rheumatological disease.	National Patient Registry.	All OHCA of any aetiology with attempted resuscitation by EMS.	≥18

Continued

Table 1 Continued

Study ID	Country	Study design	Cases	Enrolment period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Terman *et al* 2015[12]	USA	Retrospective cohort	588/558	Jan 2005–Sept 2012	Neurological outcome (CPC)	CCI (continuous), CCI=1, CCI=2, AIDS, any tumour, cardiovascular disease, chronic pulmonary disease, congestive heart failure, connective tissue disease, dementia, diabetes, diabetes (with end organ damage), hemiplegia, leukaemia/ lymphonma, mild liver disease, moderate/ severe liver disease, moderate/severe renal disease, myocardial infarction, peptic ulcer disease, peripheral occlusive vascular disease, tumour (metastatic).	Electronic health records.	All non-traumatic OHCA patients that presented to the emergency department.	≥18
Winther-Jensen *et al* 2016[14]	Europe, Australia	Post hoc analysis of clinical trial	939	2010–2013	Neurological outcome (CPC) at 6 months	Modified CCI (mCCI): mCCI=1, mCCI=2, mCCI ≥3.	Unclear.	Comatosed patients with OHCA admitted to one of 36 intensive care units with ROSC.	Unclear
Winther-Jensen *et al* 2018[39]	Denmark	Retrospective cohort	993	2007–2011	30-day mortality Neurological outcome (CPC) at discharge	Cancer.	National Patient Register.	All patients with OHCA attended to by EMS and successfully resuscitated.	≥18

CCI, Charlson Comorbidity Index; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; GCS, Glasgow Coma Scale; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, therapeutic temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2 Characteristics of included studies that did not directly compare effect of comorbidity to OHCA outcome

Study ID	Country	Study design	Cases	Enrolment Period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Beitland *et al* 2016[28]	Norway	Prospective cohort	245	Sept 2010–Jan 2014	Survival with good neurological outcome at 6 months.	Diabetes (type II) and chronic hypertension.	Hospital records	All patient with GCS <8 on admission who received TTM within 24 hours of ICU stay.	≥18
Bro-Jeppesen *et al* 2012[29]	Denmark	Prospective cohort	360	Jun 2004–Dec 2010	30-day mortality.	No comorbidities.	Unclear	All patients admitted to hospital with ROSC, GCS <9 and no cardiogenic shock.	≥18
Chen *et al* 2017[26]	Taiwan	Retrospective cohort	5338	2005–2012	Survival to hospital discharge.	CCI=1, ≥2, angina, tumour, acute myocardial infarction, cerebrovascular disease, congestive heart failure, coronary artery disease, diabetes.	Taiwan National Health Insurance database	All non-traumatic OHCA patients admitted to the emergency department.	≥18
Eid *et al* 2017[41]	USA	Cross sectional	247 684	1995–2013	Neurological outcome at hospital discharge.	mCCI=1, 2, 3, ≥4.	Nationwide Inpatient Survey (NIS)	All OHCA patients (non-traumatic) who achieved ROSC and were hospitalised.	≥18
Fabbri *et al* 2006[33]	Italy	Prospective cohort	479	Jul 1994–Dec 2004	Neurological outcome at discharge.	Hypertension, diabetes, congestive cardiac failure, myocardial infarction.	Unclear	All bystander witnessed OHCA of presumed cardiac origin.	≥18
Oh *et al* 2018[43]	Korea	Retrospective cohort	295	Mar 2007–Dec 2013	Neurological outcome (CPC).	Non-diabetic.	Registry and electronic records	All OHCA patients who achieved ROSC and were admitted to the emergency intensive care unit and were administered therapeutic cooling.	≥18
Sharma *et al* 2016[36]	Netherlands	Retrospective cohort	195	Mar 2012–Apr 2014	Survival to hospital discharge.	Atrial fibrillation, cerebrovascular accident, congestive heart failure, diabetes, dyslipidaemia/ cardiovascular conditions, hypertension, myocardial infarction, ventricular fibrillation.	Hospital records	OHCA of cardiac presumed cardiac origin in patients that survived to emergency department admission (survived means either in ROSC or ongoing CPR).	Adults

Continued

Table 2 Continued

Study ID	Country	Study design	Cases	Enrolment Period	Reported outcome	Comorbidity	Source of comorbidity data	Inclusion criteria	Age (years)
Søholm *et al* 2014[37]	Denmark	Prospective cohort	1016	2007–2011	30-day mortality.	CCI	Hospital records	All OHCA of any aetiology where patient was either in ROSC or had ongoing CPR on emergency department admission.	>18

CCI, Charlson Comorbidity Index; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; DNR, do not resuscitate; EMS, emergency medical services; GCS, Glasgow Coma Scale; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, therapeutic temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

Risk of bias within studies

Generally, the quality of studies varied greatly in regards to selection criteria and comparability. More specifically, most studies were found to be of high risk of bias with respect to comparability (ie, adjustment for confounders) and representativeness of the exposed cohort with no single study scoring well in both categories (online supplementary table 3). The majority of studies ascertained comorbidity data from hospital records however many were not clear on the type of hospital record (eg, patient clinical records or hospital billing/statistical records) or whether the record referred to prior hospitalisations or treatments. Only 12 studies[3 5 10 13 15 20 26 31 38–41] obtained history from sources that could be considered to have a low risk of exposure ascertainment bias. All studies were judged to be of low risk of bias with respect to selection of non-exposed cohort and follow-up length.

Results of individual studies

The relevant results of individual studies are reported under each of the corresponding outcome subheadings ‘Survival to hospital discharge’ and ‘Neurological outcomes after OHCA’. A request for additional data was sent to the authors of two studies[9 44] with data subsequently being provided for one[9] of these studies.

Survival to hospital discharge

Comorbidity and survival to hospital discharge/30-day survival results were provided by 19 studies.[3 5 8 9 11 13 20 26 29 31 32 34 36–40 42 44] Of these, six studies[3 8 9 26 37 38] used the Charlson Comorbidity Index (CCI)[45] as a predictor of survival. The use of CCI scores varied greatly, with some studies comparing individual CCI scores and others comparing ranges of CCI. Fifteen studies[5 8 9 11 13 20 26 31 32 34 36 38–40 44] examined the presence or absence of individual comorbid conditions as the predictor of survival.

Adjusted survival to hospital discharge results

There were 15 studies[3 5 8 9 11 13 26 29 31 34 37–39 42 44] that provided a total of 71 adjusted analyses on the association between comorbidity and survival to hospital discharge. Three studies found statistically significant decreased survival in all CCI models (where CCI >0).[8 9 37] Two studies[3 26] found that survival was not statistically different in those with a CCI ≥1 (compared with CCI=0) although these studies restricted their cohort to patients either successfully resuscitated and admitted to hospital[3] or admitted to the ED.[26] Another paper found that only higher CCI scores showed significant negative relationships.[38] Three studies[8 9 38] demonstrated monotonic trends, whereby each increase in CCI (ie, increased comorbidity), was associated with a further reduction in survival. Most individual comorbidities were predictive of lower survival. Four[9 13 34 38] out of six studies[9 13 26 34 38 44] found statistically significant lower survival to hospital discharge in patients with a prearrest history of diabetes. One[26] out of four studies[9 13 26 38] demonstrated that a history of myocardial infarction (MI)

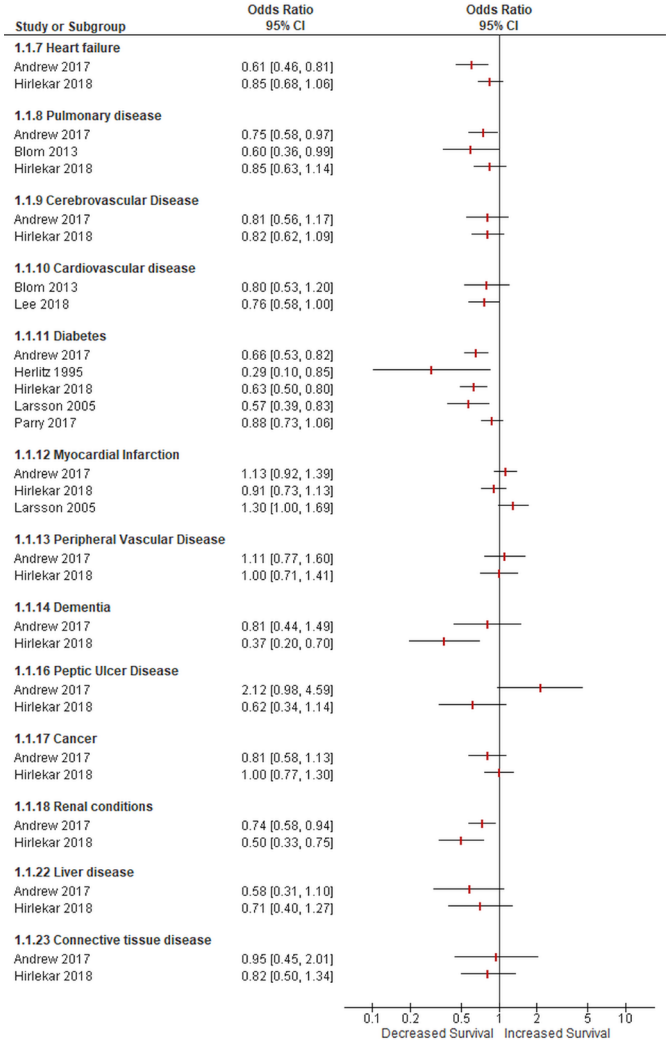

Figure 2 Forest plot showing adjusted ORs of individual comorbidities on survival to hospital discharge.

was associated with higher survival after OHCA (mortality HR: 0.80 CI: 0.68 to 0.94). One of two studies showed a slight, but non-significant, survival benefit in patients with peripheral vascular disease (figure 2).[9 38] One[13] of two[13 26] studies that looked at a prearrest history of angina pectoris showed a statistically significant increase in survival to hospital discharge. Looking more broadly at heart disease and survival following OHCA, two studies[11 26] found no significant relationship, while another found a statistically significant negative association with survival.[31] Three studies reported on the effect of cancer on survival to hospital discharge with all three studies finding no significant effect on survival.[9 38 39] One study[42] that looked at the relationship between the number of comorbid conditions and survival found that an increasing cumulative number of comorbidities resulted in decreased survival (figure 3). Finally, a single study found that patients with no prearrest comorbidity were significantly more likely to survive to hospital discharge than those with prearrest comorbidity.[29]

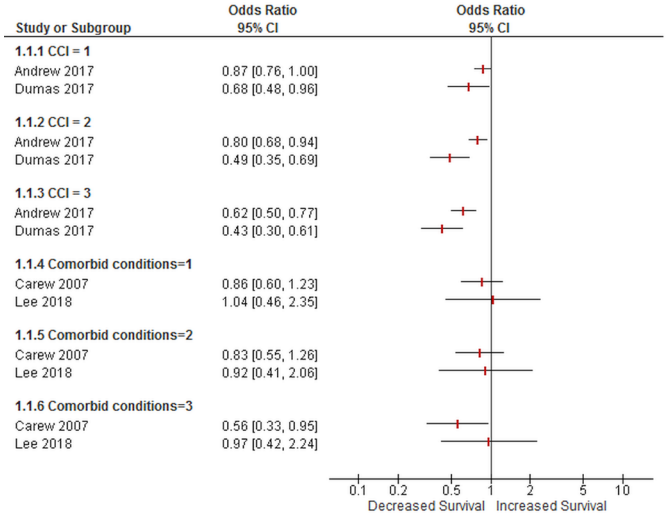

Figure 3 Forest plot showing adjusted ORs of comorbidity burden on survival to hospital discharge.

Unadjusted results for survival to hospital discharge

There were 17 studies that reported a total of 97 unadjusted analyses on the association between comorbidity and survival to hospital discharge.[3 5 8 9 11 20 26 29 31 32 34 36 37 39 40 42 44] Individual papers reported between 1[3 20 29 31 37 44] and 22[8] unadjusted results for a variety of comorbidity measures. Of all reported unadjusted results across these 17 studies, 51% (49/97) showed a statistically significant reduction in survival to hospital discharge for individuals who had a prearrest comorbidity while 4% (4/97) showed significantly higher survival. Of the remaining 44/97 non-significant results, 86% (38/44) had point estimates indicating reduced survival. Forest plots for unadjusted survival outcomes have been provided as supplementary figures (online supplementary figure 1 and online supplementary figure 2).

Neurological outcomes after OHCA

The effect of prearrest comorbidity on neurological outcome following OHCA was reported in 16 studies.[5 8 10–12 14 15 20 28 30 33 35 39 41 43 44] One study provided functional outcomes after hospital discharge, but was not included in this section as the neurological outcomes could not be deduced from the paper.[9] Eleven studies measured neurological outcome at discharge,[5 8 10–12 15 20 30 39 41 44] four studies measured it at 6 months,[14 28 35 43] and one study assessed at both discharge and 12 months.[33] Comorbidity was assessed using the CCI in six of the studies[8 10 12 15 35 41] and a modified version of the CCI was used by an additional paper.[14] The remaining nine studies[5 11 20 28 30 33 39 43 44] used the presence or absence of individual comorbidity as the predictor.

These 16 studies reported neurological outcome as either good or bad, with 12 of these[5 8 10–12 14 20 28 30 35 39 43] using a CPC of 1 or 2 to indicate good neurological outcome. Two studies used the modified Rankin Scale (mRS) as an indicator of neurological outcome with one study[15] defining a good neurological outcome as a mRS of 0–3

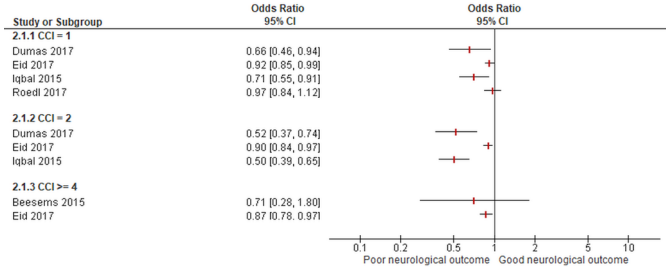

Figure 4 Forest plot showing adjusted ORs of comorbidity burden on neurological outcome.

and the other[44] defining it as a mRS of 0–2. Of the two remaining studies, one defined good outcome as patients discharged alive without International Classification of Diseases codes indicating coma, permanent anoxic brain injury or persistent vegetative state[41] and the other study defined good outcome using the Overall Performance Categories scores of 1 or 2.[33]

Adjusted results

A total of 23 adjusted analyses relating to the association between comorbidity and neurological outcome following OHCA were reported by 11 studies.[8 10–12 14 15 33 35 39 41 43] In comparison with CCI=0, a CCI=1 was significantly associated with a poorer neurological outcome in three[8 15 41] studies (figure 4) while two other studies found no significant relationship.[12 35] Similarly, CCI=2 (relative to CCI=0) was significantly associated with a poorer neurological outcome in three studies[8 15 41]; while another study found no significant relationship.[12] A 2016 study[14] showed effect estimates for the modified CCI=2 favouring a good neurological outcome, although this was not significant. Two studies found that a CCI ≥4 was associated with poor neurological outcomes[10 41]; however, this was statistically significant in only one of these studies.[41] Five studies reported individual comorbid conditions in relation to neurological outcomes (online supplementary table 2).[11 33 35 39 43]

Unadjusted results

Eleven studies provided a total of 31 unadjusted analyses on the association between comorbidity and neurological outcomes following OHCA.[5 10–12 20 28 30 33 35 41 44] Individual studies reported between 1[5 10 20 30 35 44] and 14[12] unadjusted results for a variety of comorbidity measures. Of all reported unadjusted results across these 11 studies, 29% (9/31) of results showed statistically significant poorer neurological outcomes for individuals who had a prearrest comorbidity while 3% (1/31) showed a statistically significant positive neurological outcome. Of the remaining 21 non-significant results, 62% (13/21) had point estimates indicating poorer neurological outcomes. Forest plots for unadjusted neurological outcomes have been provided as online supplementary figure 3.

DISCUSSION

This review identified 29 studies that examined the association between OHCA outcome and prearrest comorbidity. To our knowledge, this is the first systematic review to assess the association between prearrest comorbidity on both survival and neurological outcomes in patients with OHCA. We identified only one other systematic review, from 2013,[7] that overlapped the scope of our review, with several important differences. This other review[7] was restricted to patients over 70 years of age, did not examine neurological outcomes and considered comorbidity as one of a number of predictors of survival (ie, it did not focus specifically on comorbidity). This previous review[7] identified only a single paper that examined comorbidity as a predictor for survival, and concluded that more studies on comorbidity and survival were needed.

Our review found that generally the presence of prearrest comorbidity among patients with OHCA was associated with decreased survival to hospital discharge. Of the 15 included studies that presented adjusted analyses for survival to hospital discharge, 38% (27/71) reported a statistically significant negative association between comorbidity and survival, while only 3% (2/71) found a significant positive association. Furthermore, of the 42/71 remaining non-significant analyses, 62% (26/42) had point estimates indicating reduced survival, further demonstrating an overall pattern of poorer survival outcomes. Additionally, increased levels of comorbidity burden, measured using the CCI, were generally associated with a trend of decreasing survival (figure 3). With reference to individual comorbid conditions, a history of diabetes was associated with statistically significant reduced rates of survival in four[9 13 34 38] out of six studies. Despite this, no meta-analysis could be conducted between any of the studies as a result of significant clinical heterogeneity. As such, we believe the use of prearrest comorbidity as a prognostication tool for OHCA survival is unlikely to be useful which is consistent with the International Liaison Committee on Resuscitation statement.[46]

In contrast, a patient's prearrest history of MI was shown to be suggestive of increased survival to hospital discharge in three[9 13 26] out of four[9 13 26 38] studies reporting on the condition, with one[26] of the studies reporting statistically significant results. Furthermore, one[13] of two[13 26] studies found that patients with a history of angina, a condition with a similar underlying pathology to MI, had statistically increased odds of survival. The reasons for these apparent survival benefits are unclear, however it has been suggested that certain medications such as statins, routinely prescribed to patients with these conditions, may be responsible for this effect.[47–49]

The presence of prearrest comorbidity was generally associated with worse neurological outcome after OHCA. A total of 23 adjusted neurological outcome results were reported across 11[8 10–12 14 15 33 35 39 41 43] of the 29 included studies. Overall, 56% (13/23) of these adjusted results showed that individuals with prearrest comorbidity had statistically poorer neurological outcomes while no results

reported statistically positive neurological outcomes. Of the remaining 10 non-significant results, 80% (8/10) had point estimates indicating reduced neurological outcome. As with survival, we found similar variation in results between studies. When looking at cumulative comorbidity burden using CCI there was no corresponding pattern between increasing CCI and increasing odds of poorer neurological outcome. Furthermore, there was greater variation in results between studies examining neurological outcome by corresponding CCI level (figure 4) than for survival. We suspect this discrepancy could be explained by the fact that CCI is a mortality risk indicator[45] and therefore may be ineffective in assessing the effect of comorbidity burden on neurological outcomes.

Limitations

Limitations of included studies

A number of limitations within the studies included in this review were identified. First, a large proportion of studies did not stipulate specific health conditions, instead using broad descriptors such as 'heart history' or 'respiratory disease'. This ultimately made it difficult to interpret results, since many different diseases could fall within those broad descriptions. Second, many of the included studies did not adequately quantify the severity of the comorbidities within their cohorts. This was particularly noteworthy in conditions that can have a large range of physiological presentations and mortality risks such as diabetes or liver disease. Some studies did attempt to account for this. Some dichotomised conditions by severity, such as those that stratified diabetes as either 'diabetes' or 'diabetes with complications'.[3 38 40] One study attempted to account for comorbidity severity by using the Sequential Organ Failure Assessment scores,[35] while others adjusted for comorbidity severity using the CCI. Given the CCI was designed to predict 1 year mortality risk based on the presence of a predefined list of comorbid conditions, we believe it is an acceptable tool that assesses both the number of comorbidities and severity of those conditions and recommend its use in future studies on comorbidity and OHCA survival. Third, a number of authors only reported comorbidities that were found to be significantly associated with survival which resulted in a high risk of reporting bias. Lastly, the vast majority of studies were vague regarding the completeness of patient medical histories and/or only focused on a limited number of conditions. The use of incomplete or inaccurate patient history may result in large variability between studies as seen in patients with peptic ulcer disease (figure 2). This was identified as a major risk of bias in the majority of studies. Furthermore, three studies obtained prearrest comorbidity history from ambulance patient care record forms alone.[8 9 42] Comorbidity data from ambulance records may be ascertained by paramedics from a variety of sources including bystander reports and/or current patient medications which are likely to be inaccurate or incomplete.

A high degree of clinical heterogeneity was found between studies which is consistent with findings of other related OHCA systematic reviews.[7 50 51] A substantial source of clinical heterogeneity resulted from participant recruitment and inclusion criteria. Some studies included all participants in OHCA, while others specified eligibility criteria such as witnessed arrest or shockable initial rhythm. Others only recruited participants that reached specific resuscitation milestones such as ROSC, survival to ED or hospital admission. Furthermore, a number of studies only included patients with specific acute or chronic complications/conditions or those meeting specific eligibility criteria for clinical interventions. Ultimately, this heterogeneity made it inappropriate to compare outcomes between studies and prevented a meta-analysis from being conducted. This review highlights a clear need for a more standardised approach in reporting of comparative observational OHCA studies to enable the true effect of comorbidity on outcomes to be determined. Achieving this would require standardised patient study recruitment start and end points, consistent inclusion criteria, complete comorbidity histories and uniform statistical outcome reporting. To allow for future meta-analysis in observational OHCA studies we also suggest the development of a standardised guide for statistical adjustment for arrest and resuscitation factors.

Limitations of this review

This review had several limitations. First, while every effort was made to identify all relevant studies in our search we acknowledge that some relevant studies may have been inadvertently missed. Second, as the definition of comorbidity covers a broad range of conditions and severity, a set of criteria was developed to determine what would constitute 'comorbidity' for this review (see methods section). Where studies were vague or broad in their identification of comorbid conditions, clinical judgement was used to group conditions that we believed are the same or similar. Third, comorbidities were only included in forest plots if adjusted results were available from at least two studies that provided relevant ORs. Many studies provided results for both individual comorbid conditions as well as CCI. Ultimately this meant that the same patient populations may have been used in both results. Additionally, this review only used survival to hospital discharge/30-day survival as the measure for survival and did not report shorter or longer term outcomes.

Lastly, this review predominately utilised adjusted results to reduce the effects that patient-specific and arrest-specific resuscitation factors would have on the variability of results between studies. However, the list of adjustment factors varied greatly between studies (online supplementary table 1 and online supplementary table 2), with some only adjusting for one or two resuscitation factors while others adjusted for multiple prearrest/periarrest/postarrest factors. Despite this, given the clinical variability between studies we believe these results still

provide a more robust representation of the effect of comorbidity than crude results alone.

CONCLUSIONS

Despite variability between studies and reported outcomes, it appears that prearrest comorbidity is generally associated with both lower survival and poorer neurological outcomes following OHCA. Survival to hospital discharge was found to be particularly negatively associated with a prearrest history of diabetes. Few studies had point estimates of a positive association between comorbidity and survival, with the most consistent result being for MI (three of four studies having point estimates of a positive association, although only one statistically significant association). There were high levels of clinical heterogeneity between studies which precluded meta-analyses of results. Given our findings, we believe using comorbidity as a prognostication tool for determining OHCA outcomes is unlikely to be useful.

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