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Review article

Frequency of adjustment with comorbidity and illness severity scores and indices in cardiac arrest research☆

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ABSTRACT

Background: Previous research demonstrates that results from observational research correlate well with results from clinical trials, and if the former are well designed these can guide clinical practice. Observational studies in cardiac arrest research are beset by confounding due to illness severity and comorbidity. We aimed to count the number of studies that utilize comorbidity and illness severity scores and indices, and to measure the change in results across analyses that adjust for scores and indices.
Methods: A systematic search of databases for cardiac arrest studies that report survival outcomes for 2015 and that utilize illness severity and comorbidity indices and scores was conducted. We quantified the proportion of studies and the change in magnitude of estimates when adjustment for indices and scores were used.
Results: Sixty (28%) of 213 cardiac arrest studies that report survival outcomes utilize illness severity or comorbidity indices and scores, of which 39 studies (65%) used risk scores and indices to account for the confounding effect of comorbidity or illness severity. A 14% change towards the null in the magnitude of effect sizes was apparent when models included illness severity or comorbidity adjustment (interquartile range −37.7 to 4.4).
Conclusions: A small proportion of cardiac arrest studies account for illness severity and comorbidity with scores and indices, and such adjustment tend to drive estimates towards the null (no difference in groups being compared). Confounding by illness severity and comorbidity is a significant source of bias in non-randomized cardiac arrest studies.

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Introduction

Sudden cardiac arrest is a large contributor to premature death worldwide,[1] with low survival and an unacceptable functional outcome.[2] A recent report from the United States Institute of Medicine outlined key strategies to increase survival from cardiac arrest, with quality research highlighted as a strategic priority.[3] Much of the cardiac arrest research is observational in design with the inherent biases associated with observational methods. While there are multiple potential areas of bias in observational research, confounding is an increasingly recognized issue.[4,5] Confounding factors are those that are associated with the predictor of interest and the outcome, and have the ability to make a factor of interest appear worse or better at predicting the outcome than it would in reality. Despite the potential for bias due to confounding, soundly conducted observational studies can compare well with controlled trials.[5–7] If confounding and other biases are accounted for, non-randomized observational studies can produce results that approach those of controlled trials and help guide clinical practice.[8]

Comorbidity and illness severity are important confounders,[9,10] and may affect interpretation of cardiac arrest studies.[11] Comorbid diseases are illnesses that are typically chronic in nature, and have a significant impact on both short and long-term mortality.[12,13]

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Alternatively, illness severity is the risk introduced by acute prognostic factors that the patient is currently experiencing.[9] For example, the illness severity of a cardiac arrest patient with a presenting rhythm of asystole is likely to be higher than a patient with ventricular fibrillation. Sjoding et al. showed that when observational studies fail to adequately adjust for mortality risk caused by illness severity and/or comorbidities (risk adjustment) it can make a safe treatment appear unsafe, and a useful treatment seem ineffectual or even harmful.[14] They demonstrated that failure to risk adjust for sicker patients could result in odds ratios for mortality of 1.4 or more when the treatment's true effect was in fact beneficial with an odds ratio of 0.6 or 0.8.[14] Sjoding et al. verified that if a study sufficiently adjusted for risk due to the confounding effect of illness severity and comorbidity using baseline illness severity or comorbidity indictors that discriminate mortality well (area under the curve of >0.75), then such an observational study is generally protected from the confounding caused by illness.[14]

Despite these known biases and techniques to help minimize the latter, it is currently unknown how frequently *cardiac arrest* research utilises risk adjustment for the confounding effects of comorbidities and illness severity despite the existence of multiple comorbidity and illness severity scoring systems. We sought to determine the number of observational cardiac arrest studies that use or adjust for illness severity and comorbidities with designed-for-purpose indices and scores for a one-year period. We hypothesize that there are few. Furthermore, we quantified the effect of adjustment for comorbidities and illness severity on outcomes.

Methods

Two researchers (JC and FF) independently searched Medline, Embase and Cochrane Central Register of Controlled Trials for all observational cardiac arrest studies that report survival outcomes accepted for publication in all journals, for 1 January 2015 to 31 December 2015. Search terms are attached in Appendix A. Survival outcomes are those outcomes that report a proportion or incidence of a cohort that survives compared to those who do not, or those that survive longer or with an improved functional status compared to those that survive shorter or with worse functional status. Survival or health outcomes include, but are not limited to outcomes such as return of spontaneous circulation (ROSC), survival to hospital, survival to hospital discharge, survival with good neurological outcome, neurological function at hospital discharge, disability after survival, and survival time (time to death etc. from survival analysis such as one-month survival). Observational studies are defined as etiologic or effectiveness studies using data from observational analytic designs.

Four researchers (AG, JC, FF and KZ) independently reviewed abstracts for suitability, and candidate abstracts had full text reviewed against inclusion and exclusion criteria by the same four researchers. Studies were excluded if they were abstract only publications, posters, non-English, review articles, non-analytic designs, studies on manikins and simulations, or on animals. Studies were further excluded if they were not mainly cardiac arrest (≥90% of cohort), or reported no survival outcomes. Four reviewers (AG, JC, FF and KZ) searched the full text for evidence of use of or adjustment for illness severity and/or co-morbidity scores by looking for the keywords for such indices including (but not limited to):

Charlson; Age-combined Charlson Co-morbidity Index or ACCI; Deyo; Quan; Romano; Elixhauser; D'Hoore; Ghali; comorbidity; case mix or case-mix; empirical weights; Pittsburgh Cardiac Arrest Category or PCAC; Therapeutic Interventions Scoring System or TISS; Acute Physiology Age and Chronic Health Evaluation Systems or APACHE or APACHE II or APACHE III; Simplified Acute Physiology Score or SAPS; Mortality Prediction Models or MPM; Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity or POSSUM; Sequential Organ Failure Assessment or SOFA; Comorbidity-Polypharmacy Score or CPS; Diagnosis-related group or DRG; Healthcare Resource Groups or HRG; Pediatric Risk of Mortality or PRM; Pediatric Index of Mortality or PIM; Good Outcome Following Attempted Resuscitation or GO-FAR; OHCA score; Full Outline of unresponsiveness or FOUR; Cardiac Arrest Survival Post-Resuscitation In-hospital or CASPRI; index of co-existent diseases or ICED; Wright-Khan indices; Chronic Disease Score; propensity scores.

Propensity scores were grouped with illness severity scores as they are an indirect reflection of the latter through their association with treatment selection. Two researchers (JC and PF) noted the numbers of all observational studies that met the inclusion criteria, and indicated which of these have accounted for or used known illness severity and co-morbidity scores. The same researchers counted the proportion of papers that used these scores or indices and extracted adjusted and unadjusted estimates into a table. We extracted the study, description, the purpose served by the score/indices in the particular study, type of score/indices and the estimates of the model or analysis with and without the score/indices.

The impact of the comorbidity/illness severity score or indices on estimates was measured by calculating the magnitude and direction of change (+ if away from the null and − if towards the null), expressed as a percentage, of the largest model/analysis effect estimate *without* the risk indices or score compared to the largest model/analysis effect estimate *with* the risk indices or score. We only compared models if the smaller of the two models had covariates that nest entirely within the largest model or analysis regardless of whether the larger model had additional covariates other than the score/indices. We expressed the median and interquartile range of these changes across all studies, calculated using Stata version 13 (Stata Corp, College Station, Texas, USA).

Results

We identified 213 cardiac arrest studies that had an analytical design and report survival outcomes for the year 2015. Sixty (28%) of these studies addressed prognostic risk by using comorbidity and illness severity scores and indices (Fig. 1). Of these 60 studies, 39 studies (65%) used risk scores and indices to account for the confounding effect of comorbidity or illness severity in an analysis, nine studies (15%) did not use scores or indices as a predictor nor to adjust for confounding, but merely report the values in cohorts for comparative purposes. A further 12 studies (20%) utilized scores and indices as variables in a purely predictive model. Twelve studies (20%) used comorbidity scores only and 42 studies (70%) made use of an illness severity score only. Six studies (10%) utilized both a comorbidity and illness severity score and index. Of the 60 studies that used comorbidity indices the Charlson comorbidity index (28%) was the most commonly utilized, and of those that used illness severity scores, propensity scores (25%) and SOFA (20%) were the most frequent (Table 1).

Twenty-three (59%) of the 39 studies that accounted for confounding with risk scores did so in a manner that made a comparison of risk adjustment possible.[11,15–36] Across these 23 studies, we found a median −14% change (minus indicating towards the null) in the magnitude of effect sizes when models or analyses included illness severity or comorbidity adjustment (interquartile range −37.7 to 4.4%), compared to when they did not (Table 2). Fifteen of these 23 studies (65%) had estimates whose magnitude decreased after risk adjustment. One out of the 23 studies had a zero magnitude change after risk adjustment. Seven of the 23 stud-

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