Survival After In-Hospital Cardiopulmonary Resuscitation

A Meta-Analysis

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OBJECTIVE: **To determine the rates of immediate survival and survival to discharge for adult patients undergoing in-hospital cardiopulmonary resuscitation, and to identify demographic and clinical variables associated with these outcomes.**

MEASUREMENTS AND MAIN RESULTS: **The MEDLARS database of the National Library of Medicine was searched. In addition, the authors' extensive personal files and the bibliography of each identified study were searched for further studies. Two sets of inclusion criteria were used, minimal (any study of adults undergoing in-hospital cardiopulmonary resuscitation) and strict (included only patients from general ward and intensive care units, and adequately defined cardiopulmonary arrest and resuscitation). Each study was independently reviewed and abstracted in a nonblinded fashion by two reviewers. The data abstracted were compared, and any discrepancies were resolved by consensus discussion. For the subset of studies meeting the strict criteria, the overall rate of immediate survival was 40.7% and the rate of survival to discharge was 13.4%. The following variables were associated with failure to survive to discharge: sepsis on the day prior to resuscitation (odds ratio [OR] 31.3; 95% confidence interval [CI] 1.9, 515), metastatic cancer (OR 3.9; 95% CI 1.2, 12.6), dementia (OR 3.1; 95% CI 1.1, 8.8), African-American race (OR 2.8; 95% CI 1.4, 5.6), serum creatinine level at a cutpoint of 1.5 mg/dL (OR 2.2; 95% CI 1.2, 3.8), cancer (OR 1.9; 95% CI 1.2, 3.0), coronary artery disease (OR 0.55; 95% CI 0.4, 0.8), and location of resuscitation in the intensive care unit (OR 0.51; 95% CI 0.4, 0.8).**

CONCLUSIONS: **When talking with patients, physicians can describe the overall likelihood of surviving discharge as 1 in 8 for patients who undergo cardiopulmonary resuscitation and 1 in 3 for patients who survive cardiopulmonary resuscitation.**

KEY WORDS: **cardiopulmonary resuscitation; meta-analysis; resuscitation; prognosis.**
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The do-not-resuscitate (DNR) order has become well accepted and widely used in American hospitals, and for the majority of patients who die in the hospital, a DNR order has been written by the time of their death.[1–3] The decision to discuss or execute a DNR order is driven by several concerns: the patient's current quality of life, the likelihood that cardiopulmonary resuscitation (CPR) will be successful, the patient's long-term prognosis following successful resuscitation, and his or her anticipated quality of life following successful resuscitation.[4,5]

Although judgments about quality of life are best assessed by the patient, physicians have typically been relied on to provide biomedical information and estimates of prognosis; this is consistent with a shared approach to medical decision making. Information about prognosis can either be communicated implicitly (e.g., "I don't think CPR is likely to help you") or explicitly ("Patients with your condition have a less than 1% chance of surviving to discharge after CPR"). The explicit approach has been shown in two studies to influence patient decisions about DNR orders,[6,7] so it is important that prognostic information be as accurate as possible.

Recent work has shown, however, that physicians are not accurate in predicting the outcome of CPR. In fact, when presented with detailed vignettes of actual patient cases, physician predictions of the likelihood of immediate survival following CPR were no better than random guessing, with an area under the receiver-operating characteristic (ROC) curve not significantly different from 0.5.[8] An analysis with the physician prediction of the likelihood of survival as the outcome variable in a multivariate regression shows that physicians appear to have an underlying cognitive model. However, this model overemphasizes the importance of age and omits other important factors such as serum creatinine level, cancer, pneumonia, dependent functional status, and sepsis (unpublished results). Thus, patient decisions about DNR orders may be inappropriate, with the result that some patients will not receive CPR who might benefit from it and others will undergo resuscitation and its associated burden with little chance of benefit.

Pre-arrest variables, which can be measured prior to the onset of cardiopulmonary arrest, appear most useful to patients and physicians in their discussions of DNR orders. Peri-arrest variables such as the initial rhythm, duration of resuscitation, response time, and medications used have significant predictive value but are of little use when discussing DNR orders with a competent patient prior to cardiac arrest. For example, asystole as an initial rhythm and poor response time are both highly predictive of a poor outcome, but there is no way to directly measure these clinical parameters prior to the cardiopulmonary arrest.

Many studies have examined the relation between pre-arrest variables and survival following in-hospital CPR.[9–57] Sample size calculations (assuming an overall rate of immediate survival of 42%, one-sided $\alpha = 0.05$, and $\beta = 0.20$)[57]

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show that if an important predictor variable is present in 20% of patients who undergo CPR, 929 patients would have to be included in a study in order to detect an absolute difference of 10% in the rate of immediate survival. Similar calculations assuming an overall rate of survival to discharge of 16% show that 487 patients are needed to detect an absolute difference of 10% for this outcome. However, only six studies were identified in a review of the literature that reported results for more than 500 patients, and only one included more than 1,000 patients.[10,36,41,43,47,56]

Therefore, the majority of studies have had inadequate sample size to identify important predictors of the outcome of in-hospital CPR. Although smaller studies have shown relations between pre-arrest variables and the outcome of CPR, those associations have been inconsistent. For example, several studies have shown that pneumonia is a strong predictor of poor outcome,[12,37] others have not.[32,55]

Two previous meta-analyses examined the relation between pre-arrest variables and survival after in-hospital CPR.[58,59] On the one hand, meta-analyses have the advantage of greater power to detect variables associated with the outcome of CPR, and may offer greater generalizability because patients studied are drawn from several institutions. On the other hand, publication bias (studies not submitted or published if they find no association), reporting bias (data for specific variables not reported if no association is found), and interstudy variability are known limitations of this analytic technique.[60] These two meta-analyses found that the following variables are associated with a decreased likelihood of survival to discharge: age,[58,59] cancer,[58,59] cerebrovascular accident,[59] congestive heart failure,[59] homebound status,[58,59] hypotension,[59] metastatic cancer,[58] pneumonia,[58,59] sepsis,[58,59] and serum creatinine level above 130 μmol/L (1.5 mg/dL).[58,59] In addition, acute myocardial infarction on admission and a history of coronary artery disease were both associated with an increased likelihood of survival to discharge.[58,59]

These two previous meta-analyses had several limitations. First, neither addressed the issue of immediate survival following in-hospital CPR. Also, neither considered the issue of study quality or comparability of definitions when combining estimates. In addition, neither used a random effects model, which takes into account interstudy variability.[60] Finally, a number of studies published since 1990 were not included in either analysis.

The goal of this study is a meta-analysis of studies since 1980 that utilize pre-arrest variables to predict the outcome of in-hospital CPR. Two outcomes will be considered: immediate survival and survival to discharge (Fig. 1). Postdischarge survival was not studied because data are only sporadically available, and for varying lengths of time after discharge, precluding meta-analysis. Studies prior to 1980 were excluded because of changes in the technique of CPR, and more importantly because of a concern that the characteristics of resuscitated patients have changed owing to advances in technology, changes in reimbursement, and the widespread application of DNR orders.

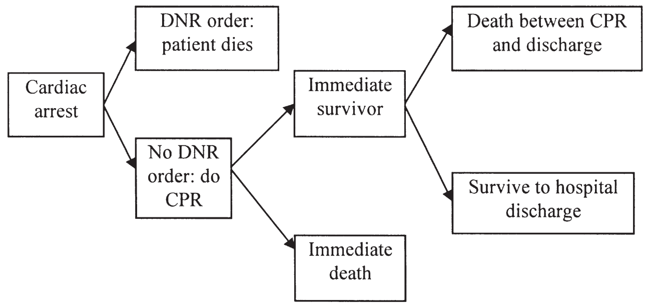

FIGURE 1. The process of in-hospital CPR.

METHODS

Definitions

Cardiopulmonary arrest is defined as the sudden cessation of spontaneous respiration and circulation leading to loss of consciousness and necessitating CPR, not including syncope, seizures, or respiratory arrest without pulselessness or loss of consciousness that responds to artificial ventilation alone. At a minimum, CPR is defined as the use of chest compressions and rescue breathing.

Survival-to-discharge patients includes those transferred to a rehabilitation facility or extended care facility, and those requiring home nursing services. Adult is defined as having reached the age of 18 years. The patient, rather than arrest, is the unit of analysis in included studies. Otherwise, a patient arresting three times and surviving to discharge would “contribute” three survivals to the analysis. It is not possible to adjust for this problem with aggregate data.

Identification of Studies

Eligible studies were identified from a search of the National Library of Medicine’s MEDLARS database using the Medical Subject Heading terms “cardiopulmonary resuscitation/all subheadings” and limited to “abstract online,” “year of publication ≥ 1980,” “human,” and “English language.” A total of 750 studies were identified in this manner. Other studies were identified from a search of each study’s list of references, and from one of the author’s extensive file of articles on CPR. Studies that did not report at least one of the outcomes of interest (immediate survival or survival to discharge of in-hospital CPR) stratified by at least one pre-arrest variable (e.g., separate estimates of survival to discharge for patients with and without metastatic cancer) were excluded, leaving 49 studies for closer review. No attempt was made to search for unpublished studies; we felt that publication bias was unlikely to be an issue because a “negative” study result is not typically possible in a descriptive study.

Inclusion Criteria

Some authors advocate a detailed analysis of the quality of each study in a meta-analysis, with a score used to assess adherence to ideal research standards.[61] Others have questioned this approach because of the inherent subjectivity of weighted scores and variation in how completely study design is reported in published manuscripts.[62] In addition, such standards are most appropriate for randomized controlled trials and other studies of intervention. This is a meta-analysis of nonrandomized studies, for which key standards such as blinding, allocation to treatment groups, withdrawals, therapeutic regimen, study administration, and method of randomization are not meaningful.

We have chosen to focus on three key aspects of study design: the population studied, the clarity of definitions, and the setting. Two sets of inclusion criteria were used, minimal and strict. The minimal inclusion criteria were studies of adult patients undergoing in-hospital CPR that measured either immediate survival or survival to discharge. Strict inclusion criteria were the minimal inclusion criteria as well as inclusion only of patients from both the general ward and intensive care unit (ICU), and provision of adequate definitions of cardiopulmonary arrest and CPR. (An adequate definition was felt by consensus of the reviewers to be consistent with the definitions of cardiopulmonary arrest and CPR described above.)

Two sets of criteria were used to better understand the association between predictor variables and key outcomes. The looser minimal criteria identify a much larger group of less homogeneous studies, but also have the benefit of a larger number of both patients and variables studied. The stricter criteria generate a set of studies that are more likely to be homogenous and are therefore more appropriate for meta-analysis, but in which the likelihood of type II error due to inadequate sample size is greater.

Data Abstraction

Each of the 49 articles initially identified was reviewed separately by two experienced family physician researchers; one researcher reviewed all of the articles, and the remaining three researchers each reviewed 16 or 17 articles. Each physician first described the demographic characteristics of each study and whether it met both the minimal and strict inclusion criteria. Then each researcher abstracted data for all variables reporting at least one of the outcomes of interest (survival to discharge or immediate survival) for patients with and without the characteristic (e.g., the rate of survival to discharge for patients with and without metastatic cancer). Data were recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Wash.).

The lead researcher compared the spreadsheets containing the results of the initial data abstraction. Differences were noted and reconciled by discussion among researchers. Studies not meeting minimal inclusion criteria as described above were removed from the spreadsheet and excluded from further analysis. Studies were excluded for the following reasons: included patients with a pulse,[10] included children,[34,46] included out-of-hospital arrests,[36,46] or duplicated data from another analysis by the same authors.[48,56] One study was excluded because only a single patient met the inclusion criteria.[49] Four of the studies included in the analysis either children[31,41] or out-of-hospital arrests,[41,42] but presented their data in such a way that these nonqualifying cases could be excluded from the analysis. A total of 41 studies met the minimal inclusion criteria, while only 10 studies met the strict inclusion criteria.[19,24,26,27,32,43,45,47,53,55]

Analysis

The rates of immediate survival and survival to discharge were graphed against the sample size (funnel plots) to determine if there was any obvious publication bias. The rates of immediate survival and survival to discharge were also graphed by the year of publication to identify any longitudinal trends.

For dichotomous variables, each variable for each study was abstracted to a contingency table; rows represented patients with and without the variable of interest (e.g., with and without cancer), and columns represented patients who survived and did not survive (e.g., survivors to discharge and patients who did not survive to discharge). The DerSimonian and Laird summary odds ratios (ORs) were calculated based on a random effects model using the software package Meta-Analyst (J. Lau, MD, New England Medical Center, 1996). Odds ratios may overestimate the relative risk when the outcome of interest (mortality in this case) is common. When the number of events in a cell was 0, a value of 0.5 was added to the event cell for both treatment and control groups. The Q statistic was used to describe the heterogeneity of studies. A value of $Q > (S - 1)$, where S is the number of studies combined, suggests substantial heterogeneity. When $Q \leq (S - 1)$, the fixed and random effects models should give similar results.[63]

For continuous variables, summary effect sizes, standard errors, and 95% confidence intervals (CIs) were calculated using software written by one of the authors using Visual Basic 4.0 for Windows (Microsoft Corporation). The effect size is a standardized estimate, calculated by taking the difference between the mean for patients having the characteristic and the mean for patients not having the characteristic, and dividing that by the standard deviation. For example, if the mean age of nonsurvivors was 70 and that of survivors was 60, with SD = 20, the effect size would be $(70 - 60)/20 = 0.5$. If the SD was equal to the mean difference,[10] the effect size would be one, whereas if the mean difference is twice the SD, the effect size is 2. The summary effect size is calculated using the method described by Hasselblad and McCrory.[60]

If available in the original literature, dichotomous outcomes are also presented for some continuous variables (i.e., age, hematocrit, and serum creatinine level) because these results may be more easily interpreted by clinicians compared with other dichotomous variables. If more than one dichotomous cutpoint is used in the original literature for a variable, both results are presented (i.e., serum creatinine level of 1.5 and 2.5).

RESULTS

Characteristics of Studies

Table 1 presents a summary of the characteristics of studies included in either the minimal or strict analysis. The 41 studies meeting the minimal inclusion criteria included 9,838 patients. The subset of 10 studies meeting the strict inclusion criteria included 2,434 patients. Among the 41 studies that met the minimal criteria, 12 took place in Europe,[13,15,17,19,28,31,38,40–44,48] one each in Australia,[22] Israel,[24] and Japan,[30] and the remaining 26 in the United States or Canada.[8,9,11,12,14,16,18,20,21,23,25–27,29,32,33,35,38,39,43,45,50–54]

Table 1. Studies Included in the Meta-Analysis*

Study	Number of Patients	Population	Cardiac Arrest Defined Clearly (Y/N)?	Setting			
				Ward	ICU	ED	OR
Studies meeting strict inclusion criteria							
Kelly et al.[19] (1986)	62	All adults	Y	x	x		
Rozenbaum & Shenkman[24] (1988)	71	All adults	Y	x	x		
Burns et al.[26] (1989)	122	All adults	Y	x	x		
George et al.[27] (1989)	140	All adults	Y	x	x		
Roberts et al.[32] (1990)	310	All adults	Y	x	x		
Ebell & Preston[43] (1993)	218	All adults	Y	x	x		
Rosenberg et al.[45] (1993)	300	All adults	Y	x	x		
Ballew et al.[47] (1994)	313	All adults	Y	x			
Bialecki & Woodward[53] (1995)	242	All adults	Y	x	x		
Ebell et al.[8] (1996)	656	All adults	Y	x	x		
Additional studies meeting minimal inclusion criteria							
Arena et al.[9] (1980)	46	Adult cancer patients	N	x	x		
Hershey & Fisher[11] (1982)	58	All adults	N	x	x	x	
Bedell et al.[12] (1983)	294	All adults	Y	x	x	x	
Gulati et al.[13] (1983)	52	Adults ≥ age 64	N	x			
Scaff et al.[14] (1984)	242	All adults	N	x	x		
Sowden et al.[15] (1984)	108	All adults	N	x	?	?	?
Suljaga-Pechtel et al.[16] (1984)	207	All adults	Y	x	x	x	?
Bayer et al.[17] (1985)	95	Adults ≥ age 65	Y	x	x		
Dans et al.[18] (1985)	88	All adults	Y	x	x	x	x
Kyff et al.[20] (1987)	243	All adults	N	x	x	x	x
Urberg & Ways[21] (1987)	121	All adults	N	x	x		
Woog & Torzillo[22] (1987)	164	All adults	Y	x	x	x	x
Raviglione et al.[23] (1988)	336	All adults	Y	x	x		?
Taffet et al.[25] (1988)	329	All adults	Y	x	x	x	
Keatinge[28] (1989)	156	All adults	Y	x	x		x
Murphy et al.[29] (1989)	259	Adults ≥ age 69	Y	x	x	x	?
Takeda et al.[30] (1989)	90	All adults; excluded critically ill	Y	x			
Hendrick et al.[31] (1990)	73	Adults and children; children excluded from meta-analysis	Y	x			
Tortolani et al.[33] (1990)	470	All adults; excluded patients with multiple arrests	Y	x	x	x	
Lazzam & McCans[35] (1991)	125	All adults	Y	x	x	x	
O'Keeffe et al.[37] (1991)	274	All adults	N	x	x	x	
Peterson et al.[38] (1991)	114	Adults in medical ICU only	Y		x		
Vitelli et al.[39] (1991)	114	Adults with cancer only	N	x	x	?	?
Landry et al.[40] (1992)	114	Adults in ICU only	Y	x			
Tunstall-Pedoe et al.[41] (1992)	2,142	Adults and children; children excluded from meta-analysis	N	x	x	x	x
Beuret et al.[42] (1993)	104	All adults	Y	x	x	x	
Juchems et al.[44] (1993)	574	All adults	N	x	x	?	?
Robinson & Hess[50] (1994)	83	All adults	N	x	x		
Tresch et al.[51] (1994)	151	All adults	N	x	x		
Warner & Sharma[52] (1994)	98	All adults	N	x	x	x	
Smith et al.[54] (1995)	55	Adults in surgical ICU only	Y		x		

**ICU indicates intensive care unit; ED, emergency department; OR, operating room.*

For the studies meeting the minimal inclusion criteria, the overall rate of immediate survival was 43.1% (95% CI 42.5%, 43.6%) and the rate of survival to discharge was 14.6% (95% CI 14.3%, 15.0%). For the subset of studies meeting the strict criteria, the overall rate of immediate survival was 40.7% and the rate of survival to discharge was 13.4%. Only five studies reported the setting to which patients were discharged;[22,29,39,40,43] of 93 patients in those studies, 73 (78.5%; 95% CI 74.2%, 82.8%) went home, 18 (19.4%; 95% CI 15.2%, 23.5%) to a nursing home, and 2 (2.1%; 95% CI 0.6%, 3.6%) to "other" settings.

Funnel plots were drawn for both immediate survival and survival to discharge for studies meeting minimal criteria. The plot for immediate survival is shown in Figure 2. The wide portion of the funnel appears to have a paucity of findings in the left side of the distribution at the base (i.e., smaller studies reporting lower rates of survival to discharge). Thus, there may be a publication bias against studies showing a low rate of immediate survival. The funnel plot for survival to discharge in Figure 3 shows a more uniform distribution without a central peak. There were not enough studies meeting strict criteria to draw meaningful funnel plots.

Plots of survival rates by year of publication for immediate survival and survival to discharge are shown in Figures 4 and 5, respectively. They show little change in the mean rate of survival over the past 15 years, although the distribution of reported rates of survival to discharge appears to have broadened since approximately 1988.

Predictors of Survival

Relatively few studies reported on continuous variables associated with survival. Among studies meeting the minimal inclusion criteria, only age was reported by more than two, and for studies meeting the strict inclusion criteria, only age was reported by more than a single study.

To identify outliers, for each predictor variable we examined the distribution of the ORs from the studies that reported information about the predictor variable. For one such variable (the presence of coronary artery disease), the OR of 9.57 from one study[27] was much higher than the ORs in the remaining studies, whether we looked at the five other studies that examined this variable and met strict criteria (range 0.41–0.67; summary OR including the outlier 0.86; 95% CI 0.38, 1.92) or the four other studies that met minimal criteria (range 0–0.96). Therefore, we

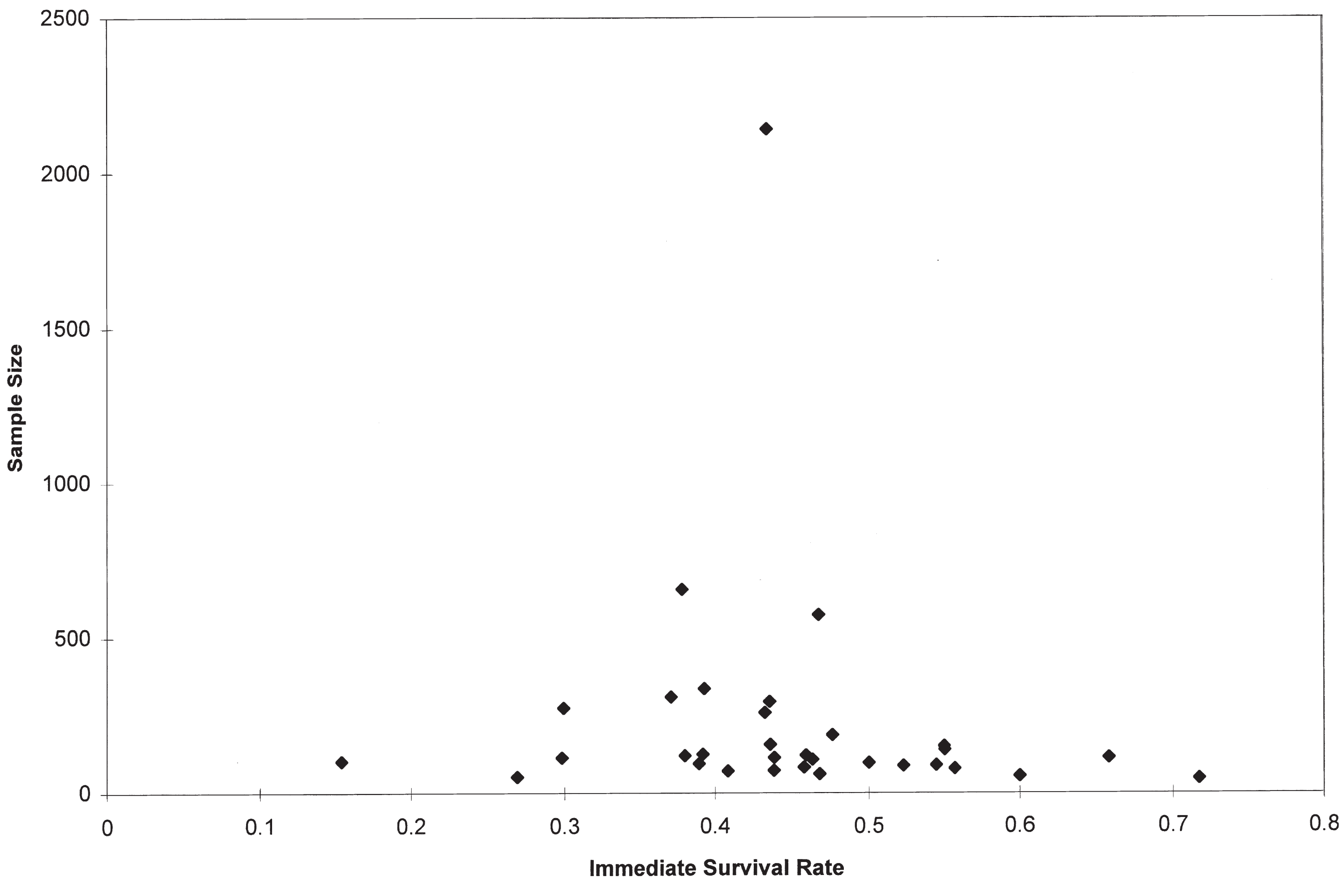

FIGURE 2. Funnel plot for studies of immediate survival following in-hospital CPR. Note the paucity of studies with small sample size and low rates of immediate survival.

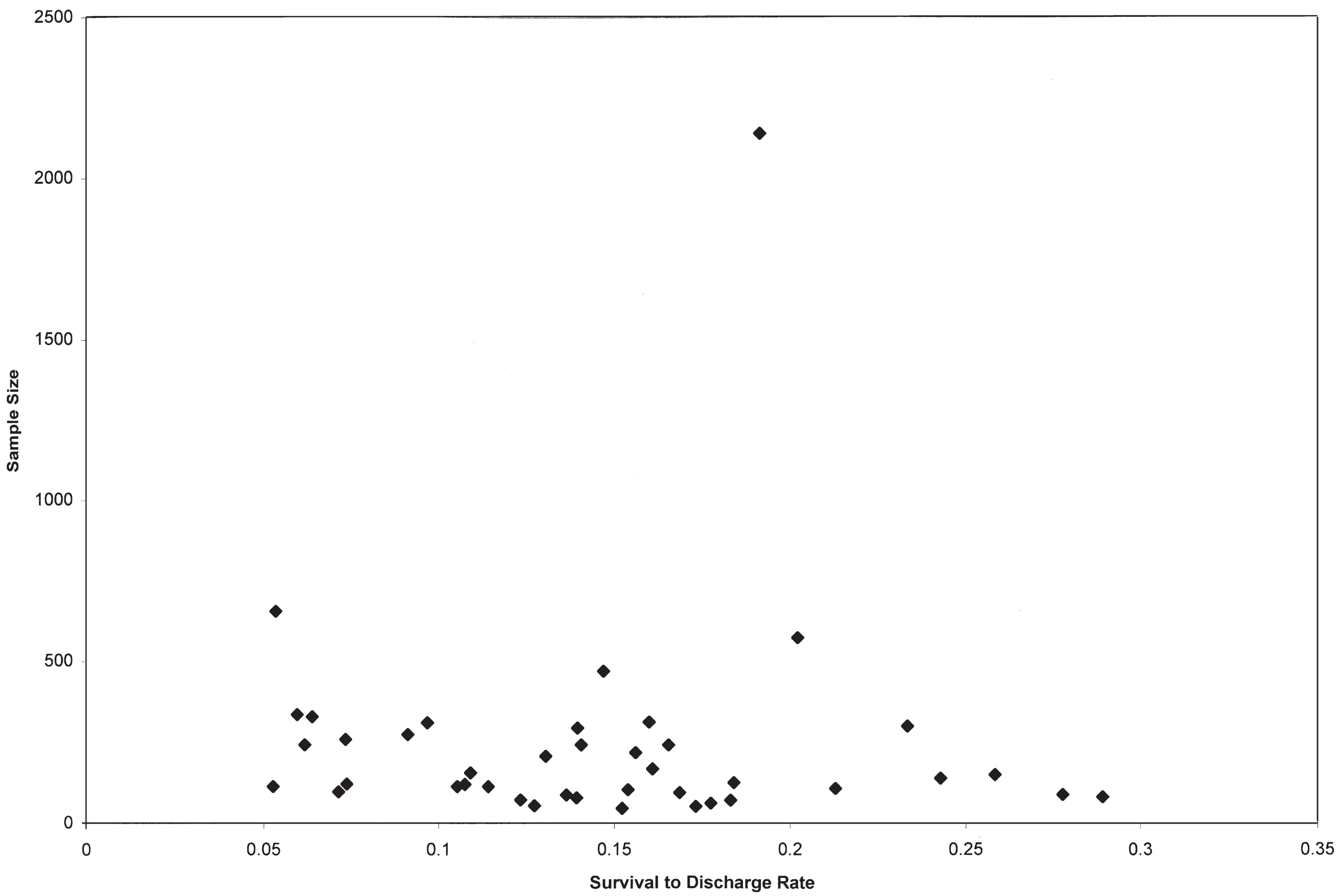

FIGURE 3. Funnel plot for studies of survival to discharge following in-hospital CPR.

did not include information about this variable from this study in the results.

Immediate Survival

Results for dichotomous variables that were significantly associated with immediate survival are summarized in Table 2. Only three variables were significantly associated with a decreased rate of immediate survival: a diagnosis of AIDS among studies meeting the minimal inclusion criteria, a hematocrit greater than 35%, and male gender among the subset meeting the strict inclusion criteria. The following dichotomous variables were not significantly associated with immediate survival in either group of studies: serum creatinine level, blood urea nitrogen, age over 70 years, presence of a third heart sound, nursing home residence prior to admission, sepsis on admission, location of the resuscitation (ICU vs ward), and diagnoses of congestive heart failure, cerebrovascular accident, cancer, metastatic cancer, pneumonia, coronary artery disease, or myocardial infarction.

Results for continuous variables are summarized in Table 3. Among studies meeting minimal inclusion criteria, an increased hematocrit was associated with a decreased rate of immediate survival. For the subset of studies meeting the strict inclusion criteria, both an increased hematocrit and a higher APACHE 2 score were associated with a decreased rate of immediate survival.

Survival to Discharge

Results for dichotomous variables significantly associated with survival to discharge are summarized in Table 2. Among studies meeting strict inclusion criteria, the following variables were associated with decreased survival to discharge: sepsis on the day before resuscitation, cancer, metastatic cancer, dementia, serum creatinine level (at cutpoints of both 1.5 mg/dL and 2.5 mg/dL), African-American race, and dependent status. Patients with coronary artery disease and location of resuscitation in the ICU were more likely to survive to discharge. Among studies meeting the minimal criteria, a similar but not identical group of variables was associated with decreased survival to discharge: cancer, metastatic cancer, dementia, serum creatinine level (at cutpoints of both 1.5 mg/dL and 2.5 mg/dL), African-American race, dependent status, age over 70 years. Patients with myocardial infarction, coronary artery disease, and hypertension had improved prognoses.

Among studies meeting strict inclusion criteria, five of six found age over 70 to be associated with failure to

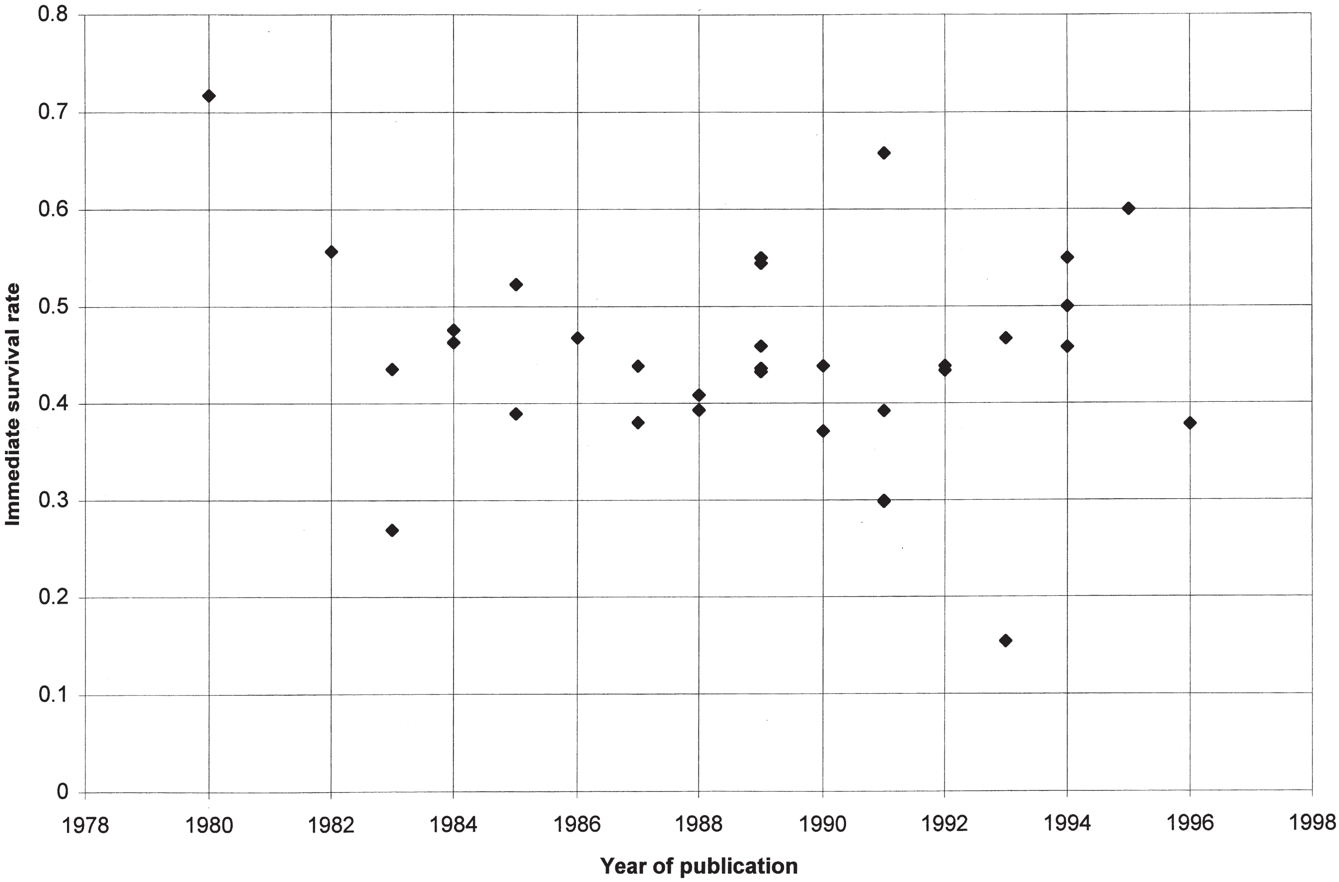

FIGURE 4. Immediate survival by year of publication.

survive to discharge, although this relation was not statistically significant (1.28; 95% CI 0.97, 1.69). Dropping the single outlier[55] resulted in a summary OR of 1.41 (95% CI 1.03, 1.91) for failure to survive to discharge. Although this was a statistically significant association, age over 70 is still not a strong predictor of failure to survive to discharge.

Results for continuous variables are summarized in Table 3. For studies meeting strict inclusion critieria, no variables were associated with survival to discharge. Among studies meeting minimal inclusion criteria, both an increased APACHE 2 score and a decreased mean arterial pressure were associated with a decreased rate of immediate survival.

The following variables were not associated with survival to discharge in either group of studies: blood urea nitrogen level, systolic blood pressure, gender, hematocrit above 35%, nursing home residence prior to admission, and diagnoses of AIDS, congestive heart failure, pneumonia, sepsis on admission, cerebrovascular accident, and diabetes mellitus.

DISCUSSION

This meta-analysis identified patient characteristics associated with both immediate survival and survival to discharge. Because of the greater homogeneity of studies meeting strict criteria, we will focus on the results for studies meeting the strict inclusion criteria.

Overall Rates of Survival

The overall rate of immediate survival for the subset of studies meeting the strict criteria was 40.7%, and the rate of survival to discharge for the same group of studies was 13.4%. When talking to patients, physicians can therefore describe the overall likelihood of immediate survival as "4 out of 10" or "2 out of 5," and the likelihood of survival to discharge as "1 in 3 for those patients who are revived" or "1 in 8 among all patients who undergo CPR in the hospital."

Despite major changes in the use of DNR orders, intensive care, and hospital services in general, the rates of immediate survival and survival to discharge have remained relatively constant over the past 15 years (Figs. 4 and 5). One would expect that increasing use of DNR orders would result in a more appropriate use of CPR, and higher survival rates. This assumes that physicians can accurately identify patients who are more likely to benefit from CPR, and that decisions about CPR are based on prognosis alone. Neither may be true; a recent study by one of the authors showed that physicians were unable to predict the outcome of in-hospital CPR when given a series of clinical

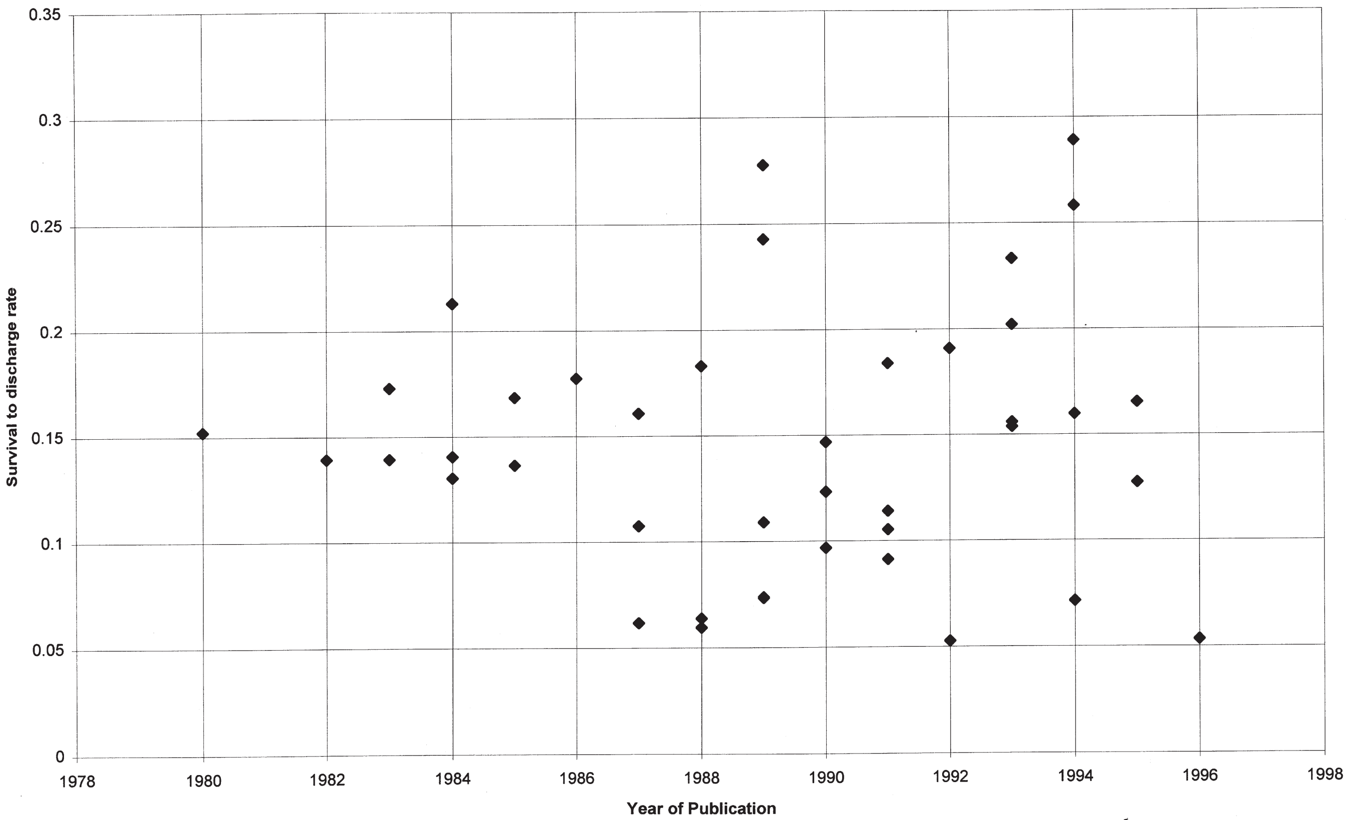

FIGURE 5. Survival to discharge by year of publication.

vignettes for which the outcomes were known to the investigators.[8] Also, decisions about CPR are clearly driven by concerns about quality of life that may not be related to prognosis.

Predictors of Immediate Survival

None of the variables associated with survival to discharge, such as metastatic cancer, impaired renal function, and dementia, was associated with immediate survival following in-hospital CPR. Only male gender, a diagnosis of AIDS, an increased hematocrit, and an increased APACHE 2 score (a measure of acute physiologic derangement) were associated with a decreased likelihood of immediate survival. It is unclear why an increased hematocrit or male gender should be associated with a poor outcome. These findings may be an example of a type I error in the single study in which a significant association was reported,[55] they may represent a reporting bias (failure of authors to report nonsignificant results), or it may be that gender and increased hematocrit represent intervening variables for tobacco use. Further study is needed to identify whether there is a relation between tobacco use and immediate survival following CPR, and to confirm or refute the association between gender, hematocrit, and immediate survival. Until that time, these findings should be considered preliminary.

Results for immediate survival were reported by only a handful of studies. The ability to predict this outcome distinct from survival to discharge may be valuable to patients who want to have a brief interval to settle affairs or bid farewell to their loved ones. Much more work is needed to identify other predictors of this outcome, and to determine whether an increased hematocrit and male gender are actually associated with a poor outcome.

Predictors of Survival to Discharge

The variable most strongly associated with failure to survive to discharge was sepsis on the day before resuscitation. However, this was only reported by one study meeting the strict criteria, and by two meeting the minimal criteria. Interestingly, sepsis on the day of admission was not a significant predictor of survival. This finding is clinically reasonable because many patients who are not septic on admission develop sepsis later during their hospital stay, as their illness worsens. Clinical prediction rules that include sepsis should therefore recalculate the patient's risk each day, in order to take into account changes in the patient's clinical status.

Cancer, metastatic cancer, dementia, dependent status, location of resuscitation on the general ward (rather than ICU), elevated serum creatinine level, and no history of coronary artery disease were all associated with failure to survive to discharge after in-hospital CPR. The association with coronary artery disease (these patients are more likely to survive to discharge) may be confounded by the

Table 2. Association Between Dichotomous Variables and Survival

	Minimal			Strict		
Variable	Studies/Patients, n/n	Heterogeneity (Q)	Failure to Survive OR (95% CI)*	Studies/Patients, n/n	Heterogeneity (Q)	Failure to Survive OR (95% CI)*
Immediate survival						
AIDS	2/992	0.28	2.52 (1.25, 5.08)†	1/656	NA	4.31 (0.53, 35.26)
Male gender	4/1,072	7.37	1.08 (0.68, 1.70)	1/656	NA	1.64 (1.19, 2.26)†
Hematocrit > 35%	1/639	NA	1.38 (1.07, 70)	1/639	NA	1.38 (1.07, 70)
Survival to discharge						
Sepsis on day prior to resuscitation	2/427	1.82	7.83 (0.73, 84.22)	1/313	NA	31.33 (1.91, 515.15)†
Metastatic cancer	10/2,367	2.69	4.79 (2.01, 11.40)†	5/1,497	0.76	3.89 (1.21, 12.58)†
Dementia	3/760	1.39	2.71 (1.01, 7.30)†	2/604	0.80	3.10 (1.08, 8.85)†
Serum creatinine > 2.5 mg/dL	3/1,146	3.79	3.14 (1.13, 8.72)†	2/868	2.77	3.08 (0.52, 18.34)
African American	1/656	NA	2.76 (1.36, 5.58)†	1/656	NA	2.76 (1.36, 5.58)†
Dependent status	8/1,152	16.72	2.75 (1.24, 6.10)†	1/140	NA	2.29 (0.81, 6.47)
Serum creatinine > 1.5 mg/dL	5/1,447	6.07	3.36 (1.66, 6.79)†	2/868	0.56	2.17 (1.23, 3.81)†
Cancer (all)	18/3,733	10.33	2.18 (1.49, 3.18)†	8/2,240	2.50	1.93 (1.23, 3.04)†
Age > 70 years	12/3,288	19.27	1.45 (1.07, 1.96)†	6/1,935	3.36	1.28 (0.97, 1.69)
Myocardial infarction	12/2,201	13.30	0.70 (0.49, 0.99)†	7/1,770	7.49	0.83 (0.54, 1.28)
Coronary artery disease (all studies)	10/2,450	48.0	0.62 (0.32, 1.20)	6/1,869	37.5	0.86 (0.38, 1.92)
Coronary artery disease (minus single outlier)‡	9/2,310	12.58	0.41 (0.27, 0.62)†	5/1,729	1.17	0.55 (0.41, 0.76)†
Location ICU	10/4,184	40.24	0.72 (0.43, 1.21)	4/1,296	1.17	0.52 (0.35, 0.78)†
Hypertension	3/505	1.26	0.48 (0.28, 0.84)†	2/384	1.23	0.51 (0.24, 1.10)

* *Odds ratio shown are for failure to survive at each outcome; a higher odds ratio indicates a* lower *chance of survival. The random effects model of DerSimonian and Laird was used to calculate odds ratios where data are combined from multiple studies. Studies are listed in order from highest to lowest likelihood ratio for their association with failure to survive to discharge in the analysis of studies meeting the strict inclusion criteria. NA indicates not applicable.*

† *Statistically significant at the 95% confidence level.*

‡ *Odds ratio shown was calculated after one outlier (George et al.) was dropped; see text for discussion.*

fact that these patients are more likely to be placed in the ICU or other monitored unit. Although the association for dependent status among studies meeting strict criteria was not statistically significant, only one such study (with 140 patients) reported data for this variable.[21] Patients having these characteristics are less likely to benefit from CPR, and this information should be communicated in a sensitive manner during DNR discussions.

A single study, by one of the authors of this meta-analysis, found an association between African-American race and survival to discharge. This study included over 300 African-American patients, the largest number studied, and was therefore the first study with adequate power to detect such an association. The association persisted after adjustment for age, comorbidities, renal function, severity of illness as measured by the APACHE 3 score, and other clinical variables.[55] More study is needed to confirm or refute this disturbing finding, and better understand the reasons for it.

Age is at best a weak predictor of the outcome of in-hospital CPR. This meta-analysis found that age as a continuous variable was not associated with immediate survival. Although age over 70 years as a dichotomous variable was associated with failure to survive to discharge among studies meeting the minimal inclusion criteria, this association was not statistically significant among the subset of studies meeting the strict inclusion criteria. This observation most likely reflects the physiologic and functional heterogeneity among the elderly, and may be confounded by comorbidity. It is therefore important that physicians look beyond a patient's biological age, and consider the presence or absence of variables more strongly associated with the outcome of CPR when discussing DNR orders with patients.

Pneumonia has been variably associated with survival to discharge. For example, Bedell et al. initially found a strong relation between the diagnosis and failure to survive to discharge after CPR,[12] although others have not always duplicated this finding.[15,21,40,55] In the current meta-analysis, pneumonia was not significantly associated with either immediate survival or survival to discharge. Certainly, differences in the criteria for diagnosis may affect

Table 3. Association Between Continuous Variables and Survival

Variable	Studies/Patients, *n/n*	Summary Effect Size	Lower CI	Upper CI
Immediate survival				
Strict inclusion criteria				
Age	2/778	−0.041	−0.19	0.10
Serum creatinine	1/646	−0.031	−0.19	0.13
Hematocrit	1/639	−0.23	−0.39	−0.067*
Mean arterial pressure	1/653	−0.013	−0.17	0.15
Minimal inclusion criteria				
Age	3/892	−0.0434	−0.17919	0.092393
Serum creatinine	1/646	−0.031	−0.19023	0.128231
Hematocrit	1/639	−0.227	−0.38743	−0.06657*
APACHE 2 score prior to admission	1/114	−0.647	−1.05813	−0.23587*
Mean arterial pressure	1/653	−0.013	−0.17102	0.14502
Survival to discharge				
Strict inclusion criteria				
Age	1/656	0.2	−0.14	0.54
Serum creatinine	1/646	−0.27	−0.61	0.071
Hematocrit	1/639	−0.04	−0.38	0.30
Mean arterial pressure	1/653	0.22	−0.12	0.56
Minimal inclusion criteria				
Age	6/1,499	−0.15	−0.32	0.015
Serum creatinine	2/701	−0.15	−0.32	0.015
Hematocrit	2/694	−0.05	−0.36	0.26
APACHE 2 score prior to admission	2/228	−1.87	−2.38	−1.36*
Mean arterial pressure	2/708	0.34	0.028	0.66*

**Statistically significant at the 95% confidence level.*

these results. This problem may apply to other clinical diagnoses such as congestive heart failure and sepsis, which have also been variably associated with the outcome of CPR.

A number of variables were significantly associated with survival to discharge in the studies meeting the minimal inclusion criteria, but not in the subset of studies meeting the strict inclusion criteria. In some cases, this may simply be due to type II error (insufficient sample size). For example, only one study each meeting the strict inclusion criteria reported data for systolic blood pressure below 100 mm Hg, third heart sound, or dependent status, and only two studies each for hypertension and dementia. Therefore, future studies should continue to look for a possible association between these variables and survival to discharge after in-hospital CPR.

Limitations of this Study

This meta-analysis has several limitations related to the design and quality of the original studies. First, some of the variables used to predict the outcome of CPR were not clearly defined in many of the studies. Examples include coronary artery disease and cancer. For the former, the vast majority of studies defined coronary artery disease by history as recorded in the medical record. Regarding the diagnosis of cancer, most studies used the medical record, and excluded basal cell carcinomas and patients with distant (less than 5–10 years) diagnoses that are now considered cured. Second, every study of in-hospital CPR included only patients who actually underwent CPR. Patients who had a DNR order written before their first episode of CPR were not included, which might bias the results. However, because these patients did not undergo CPR, we do not know whether they would have survived the intervention, and have no way of including them in calculations of ORs for survival.

Third, although some authors reported all data, others reported only the results for pre-arrest variables significantly associated with survival. This creates a kind of publication bias. Fourth, the nature of the data necessitated the use of ORs rather than relative risk calculations, which may overestimate the OR when the outcome of interest is common. This is especially a concern among studies of immediate survival, in which the frequency of mortality was over 40%. Finally, because some of the studies may have had adjusted OR estimates for potential confounders while others did not, we did not necessarily combine fully adjusted ORs. For example, patients with coronary artery disease are more likely to be admitted to a monitored unit, which may explain part of the "benefit" of this diagnosis. It is therefore important that readers not overinterpret the magnitude of the ORs presented in this meta-analysis.

Table 4. Guidelines for Future Studies of Survival After In-Hospital Cardiopulmonary Resuscitation

1. Have an adequate sample size.
2. Use clear definitions of cardiopulmonary arrest and resuscitation.
3. Use explicit inclusion and exclusion criteria.
4. Provide full demographic information.
5. Report results separately for patients from the general ward and intensive care units.
6. Report all results, whether or not statistically significant.
7. Use outcomes recommended by the Utstein Style Task Force, including at a minimum survival to discharge.
8. Patients should be the unit of analysis for studies reporting survival to discharge or survival beyond hospital discharge; and resuscitation events, the unit of analysis for studies reporting immediate survival.

Guidelines for Future Research on Survival After In-Hospital CPR

During the literature review, we identified many of the limitations of the existing body of literature. These limitations include inadequate sample size, missing or inadequate definitions, variable inclusion and exclusion criteria, differing settings, and a variety of clinical end points. We therefore propose that the sample size of future studies should be at least 500, which is adequate to detect an absolute difference of 10% in survival to discharge ($\alpha = 0.05$, $\beta = 0.20$). Also, researchers should clearly define cardiopulmonary arrest and CPR, and follow the Utstein style recommendations for research on in-hospital resuscitation.[64]

Meta-analysis would be facilitated by more complete reporting of the results for all predictor variables, and by separate reporting of results for the general ward, ICU, and other locations. Also important is the use of a standard set of clinical end points. The Utstein Style Task Force recommends reporting the duration of return of spontaneous circulation for patients who died in hospital (<20 minutes, 20 minutes to 24 hours, and >24 hours), the rates of survival to discharge, survival to 6 months, and survival at 1 year for patients who survive to discharge.[64] Our guidelines for designers of future studies are summarized in Table 4.

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