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DO NOT RESUSCITATE ORDERS AND AGING: IMPACT OF MULTIMORBIDITY ON THE DECISION-MAKING PROCESS

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Abstract: *Background:* The "Do Not Resuscitate" orders (DNR) are defined as advance medical directives to withhold cardiopulmonary resuscitation during cardiac arrest. Age-related multimorbidity may influence the DNR decision-making process. Our objective was to perform a systematic review and meta-analysis of published data examining the relationship between DNR orders and multimorbidity in older patients. *Methods:* A systematic Medline and Cochrane literature search limited to human studies published in English and French was conducted on August 2012, with no date limits, using the following Medical Subject Heading terms: "resuscitation orders" OR "do-not-resuscitate" combined with "aged, 80 and over" combined with "comorbidities" OR "chronic diseases". *Results:* Of the 65 selected studies, 22 met the selection criteria for inclusion in the qualitative analysis. DNR orders were positively associated with multimorbidity in 21 studies (95%). The meta-analysis included 7 studies with a total of 27,707 participants and 5065 DNR orders. It confirmed that multimorbidity were associated with DNR orders (summary OR = 1.25 [95% CI: 1.19–1.33]). The relationship between DNR orders and multimorbidity differed according to the nature of morbidities; the summary OR for DNR orders was 1.15 (95% CI: 1.07–1.23) for cognitive impairment, OR=2.58 (95% CI: 2.08–3.20) for cancer, OR=1.07 (95% CI: 0.92–1.24) for heart diseases (i.e., coronary heart disease or congestive heart failure), and OR=1.97 (95% CI: 1.61-2.40) for stroke. *Conclusions:* This systematic review and meta-analysis showed that DNR orders are positively associated with multimorbidity, and especially with three morbidities, which are cognitive impairment, cancer and stroke.

Key words: Do not resuscitate orders, morbidities, older adults.

Introduction

The "Do Not Resuscitate" orders (DNR) are defined as advance medical directives to withhold cardiopulmonary resuscitation during cardiac arrest (1). Such decisions are taken by medical teams for patients who could not benefit from advanced life support, in agreement with patients and their relatives (2, 3). Although the DNR orders are influenced by many factors such as patients' health status, cultural and/or societal factors (4, 8), this kind of decision will become more and more common due to the growing number of older patients with poor vital and functional status (1, 3, 9). For instance, older patients may have severe cognitive or functional impairments after a cardiopulmonary resuscitation (4-6). In order to limit this risk of poor quality of life, DNR orders should be considered before starting resuscitation (7).

Multimorbidity is frequent with the advance in age and is associated with higher rates of mortality, functional impairment and poorer quality of life (10). Thus, we hypothesized that multimorbidity could influence the decision of DNR. The purpose of this systematic review and meta-analysis was to systematically review and quantitatively synthesize the evidence connecting DNR orders with multimorbidity in older patients.

Methods

Literature search

A systematic Medline literature search limited to human studies published in English was conducted on August 2012, with no date limits. We used the Medical Subject Heading "resuscitation orders" OR "do-not-resuscitate" combined with "aged, 80 and over" combined with "comorbidities" OR "chronic diseases". The search also included the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, and Cochrane Controlled Trials). An iterative process was used to ensure that all relevant articles were obtained. A further hand search of bibliographic references of extracted papers and existing reviews was also conducted to identify studies not captured in the electronic database searches.

Study selection and analysis

One member of the team (LDD) screened abstracts from the initial search and identified articles deemed potentially relevant using the following criteria: 1) observation studies (including case series, cross-sectional, case-control, and cohort studies); 2) intervention studies; and 3) data collection of morbidities, advanced patient age, and DNR as outcomes. If a study met the initial selection criteria or its eligibility could not be determined from the title and abstract (or abstract not provided), the full text was retrieved and was independently assessed by two

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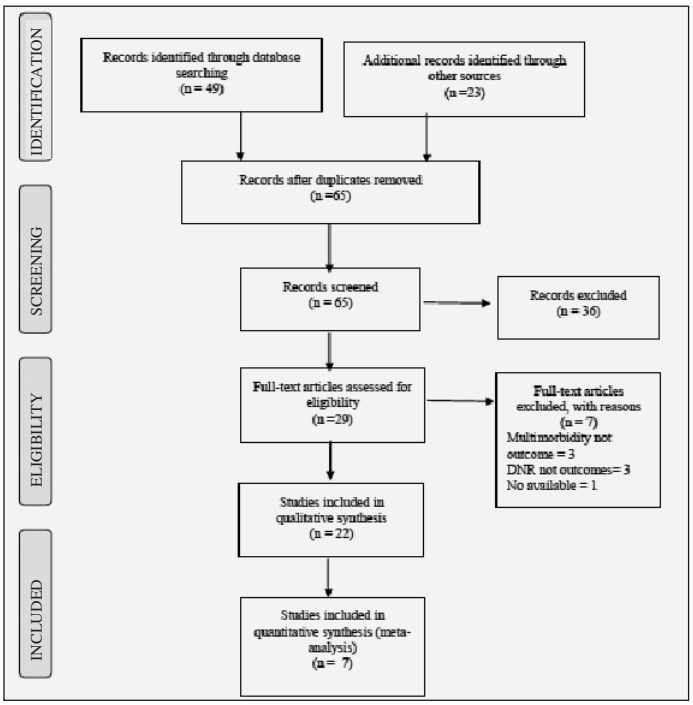
reviewers (LDD and OB) for inclusion. The full articles were screened using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist for items that should be included in reports of cohort studies and the Consolidated Standards of Reporting Trials (CONSORT) statement for clinical trials. Disagreements were resolved by a third reviewer (CA). Final selection criteria were applied when morbidities and DNR orders were used as primary outcomes. The study selection process is shown in Figure 1.

Figure 1

Flow diagram for selection of studies focusing on the association between DNR orders in older patients and multimorbidity



Of the 65 originally identified abstracts, 29 (44.6%) met the initial inclusion criteria. Seven (24.1%) of the 29 studies were excluded because multimorbidity or DNR orders were not used as primary outcomes or the study was not available. The remaining 22 studies were included in this review (1-4, 6-9, 11-24), and the following information was extracted: authors, publication date, study design, settings, study population, description of morbidities and main results.

A fixed-effects meta-analysis was performed on the estimates to generate summary values. Statistical tests of homogeneity were performed using Cochran's chi-square test for homogeneity (Q) and the percentage of total variation across studies attributable to heterogeneity (I2). Statistical analysis was performed using Computer Programs for Epidemiologists (WINPEPI) version 11.19.

Results

Table 1 summarizes the 22 studies included in this review (1-4, 6-9, 11-24). Data collection was based on 18 cross-sectional studies (2-4, 6, 8, 9, 11-21, 23) and 4 observational cohort studies (1, 7, 22, 24). The number of participants ranged from 37 to 17,440 (2, 24). Women represented 0.6-78.0% of the participants (6,20). Most of participants were inpatients (1-3, 7, 8, 11-14, 18, 20-24) hospitalized in dialysis center (23), intensive care unit (12, 22, 24), emergency (2) or burn departments (13). Other participants were institution-dwellers (4, 6, 9, 15-17, 19).

Mean age ranged from 60±16 years to 86.5±6.6 years (3,2 3). multimorbidity was assessed with several approaches: 1) qualitative approach considering the nature of the morbidity (ie, cardiac, renal, liver, respiratory, neurological, lung, vascular disease, cancer, diabetes, dementia, cognitive impairment, depression, immunodeficiency, and stroke) (1, 2, 4, 6-9, 11, 13-18, 20, 21, 24); or 2) quantitative approach considering the number of morbidities or using quantitative scales (Charlson comorbidity index) (3, 4, 9, 12, 16, 19, 22-24). In one study, DNR orders were compared between patients with different multimorbidities (cognitive impairment versus cancer) (17). DNR orders generally increased with the presence of multimorbidities (1, 2, 6-9, 11, 13-15, 18, 20, 21, 24), their increased number or their increased burden (12,19,22-24), except in one study (16). Cancer (1, 8, 18, 20, 21), cognitive impairment (2, 4, 6-9, 18, 20, 21), heart diseases (14, 15, 18, 20, 21, 24) and stroke (6, 11, 14, 18) were associated with DNR orders.

To facilitate comparison of results across published studies, a meta-analysis was performed. The summary odds ratio (OR) for DNR according to the presence of any morbidity was 1.25 (95% CI: 1.19–1.33; Q=213.91, df =13, P<0.001; I2=93.9%) (1, 4, 9, 11, 14, 15, 18). Regarding the nature of the morbidities (Figure 2), the summary OR for DNR orders was 1.15 (95% CI: 1.07–1.23) for cognitive impairment (4, 9, 18), OR=2.58 (95% CI: 2.08–3.20) for cancer (1, 9, 18), OR=1.07 (95% CI: 0.92–1.24) for heart diseases (11, 14, 15, 18), and OR=1.97 (95% CI: 1.61-2.40) for stroke (11, 14, 18).

Discussion

Our findings report a direct association between DNR orders and multimorbidity in older patients, and show that this association depends on the nature of morbidities. In particular, cancer, cognitive impairment and stoke, but not heart diseases, were positively associated with DNR orders.

We found that the risk of DNR orders was 1.25-fold higher with the presence of multimorbidity, regardless of their nature. Different explanations may be proposed for this result. First, the accumulation of morbidities in older patients may limit the use of advanced life support because of induced disability and shorter life expectancy, and may facilitate the DNR decision-

Table 1
Main characteristics of studies included in the systematic review

References	Design	Settings/Population	Definition and nature of Multimorbidities	Association between DNR and multimorbidity?
Prospective studies				
Wrenn et al, 1992 (2)	Cross-sectional study	Inpatients, Emergency department N = 37 Mean age: 70y. Women = 22 (59%)	Chronic heart disease, chronic neurologic disease, dementia, stroke, AIDS, cancer, Chronic renal failure	Yes Dementia
Jayes et al, 1993 (24)	Cohort study	Inpatients, ICU N = 17,440 Mean age DNR group: 68.5±0.4y Women DNR group: 49%	Cardiac, renal, or respiratory disease, cognitive impairment, cancer Number of morbidities	Yes Number of morbidities and Cardiac, renal, or respiratory disease,
Mark et al, 1995 (6)	Cross-sectional study	Nursing home N = 1723 Mean age: 84.7±8.4y Women: 78%	Cognitive impairment	Yes For patients with severe cognitive impairment
Shepardson et al, 1997 (1)	Cohort study	Inpatients, stroke N = 13,337 Mean age: 72±13y Women: n = 7378 (55%)	Renal disease, respiratory disease, cancer, diabetes, ischemic heart disease	Yes Cancer, OR = 2.73 with 95%CI (2.08–3.59)
Moss et al, 2001 (23)	Cross-sectional study	Dialysis center N = 469 Mean age: 60±16y Women: 54%	Number of morbidities	Yes
Jackson et al, 2004 (11)	Cross-sectional study	Inpatients, acute myocardial infarction, N = 4621 Mean age DNR group: 81y	Diabetes, cardiac, neurological, renal, respiratory, lung, cerebrovascular, or liver disease, cancer; depression	Yes Diabetes, OR = 1.25 with 95%CI (1.03–1.53); Cerebrovascular disease, OR = 2 with 95%CI (1.56–2.55); Angina, OR = 0.78 with 95%CI (0.63–0.91); Hypertension, OR = 0.83 with 95%CI (0.68–1.01)
Baccheta et al, 2006 (12)	Cross-sectional study	Inpatients, death in ICU, N = 410 Mean age DNR: 69.9±1.1y	Medical history score: number of morbidities	Yes
Nathens et al, 2008 (22)	Cohort study	Inpatients, ICU N = 6765 Two groups: <55y vs >55y	Charlson index score	Yes Patients >55 y, OR = 1.20 with 95%CI (1.09–1.30)
Lo et al, 2010 (4)	Cross-sectional study	Nursing home N = 201 Mean age: 79.98±10.47y Women: 61%	Cognitive impairment (MMS<25), cancer, number of morbidities	Yes Cognitive impairment, OR = 1.1 with 95%CI (1.03–1.18)
Retrospective Studies				
Bedell et al, 1986 (21)	Cross-sectional study	Inpatients N = 521 Mean age DNR: 73y Women DNR: n = 233 (60%)	Cognitive impairment, cancer, cardiac disease, diabetes, chronic pulmonary disease, and cerebrovascular disease	Yes Cognitive impairment, cancer, cardiac disease, diabetes, chronic pulmonary disease, and cerebrovascular disease
Schwartz et al, 1986 (8)	Cross-sectional study	Inpatients N = 174 Mean age DNR: 72.9±15.1y	Cancer, cognitive impairment	Yes Cancer, cognitive impairment
Holtzman et al, 1994 (9)	Cross-sectional study	Nursing home N = 1605 Mean age: 83.6y Women: 22%	Cancer, dementia, Charlson index	Yes Dementia, OR = 1.44 with 95%CI (1.05–1.97); Cancer, OR = 0.85 with 95%CI (0.52–1.38); Charlson index, OR = 1.00 with 95%CI (0.89–1.11)
Wenger et al, 1995 (7)	Cohort study	Inpatients N = 473 Mean age: 79y Women: 57%	Multimorbidities conditions	Yes Dementia

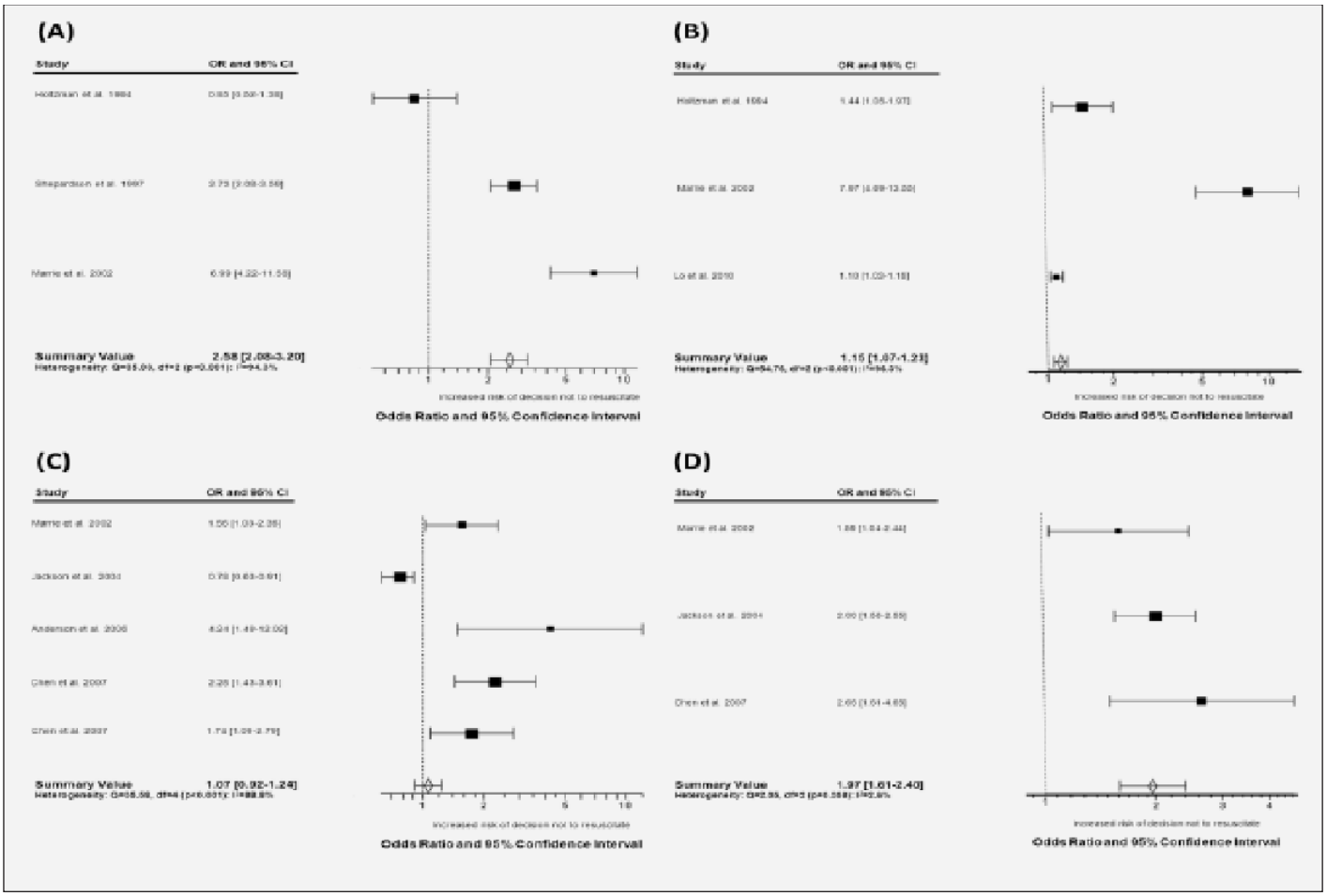
Table 1 (continued)

References	Design	Settings/Population	Definition and nature of Multimorbidities	Association between DNR and multimorbidity?
Ghusn et al, 1997 (20)	Cross-sectional study	Inpatients, cardiopulmonary arrest N = 261 Mean age DNR: 61.7± 13.6y Women DNR: 0.6 %	Congestive heart failure, coronary artery, neurological, renal, or pulmonary disease; Dementia, cancer, AIDS	Yes Dementia, cancer, coronary artery disease, chronic pulmonary disease, chronic renal and AIDS
Vaughn et al, 2000 (19)	Cross-sectional study	Nursing home N = 423 Mean age: 83±9 y Women: 70%	Charlson index score	Yes
Marrie et al, 2002 (18)	Cross-sectional study	Inpatients after pneumonia N = 1339 Mean age DNR: 79.1± 11.8y Women DNR: n = 143 (48%)	Congestive heart failure, renal or liver disease, cancer, cerebrovascular disease, dementia	Yes Cancer, OR=6.99 with 95%CI (4.22–11.58); Dementia, OR=7.97 with 95%CI (4.69–13.55); Neuromuscular disorders, OR = 2.56 with 95%CI (1.70–3.86); Cerebrovascular disease, OR = 1.59 with 95%CI (1.04–2.44); Congestive heart failure, OR = 1.56 with 95%CI (1.03–2.36)
Mitchell et al, 2004 (17)	Cross-sectional study	Nursing home patients with dementia or terminal cancer N = 2492 Mean age: dementia, 83.5±7.1 y; terminal cancer, 79.1±7.2y Women: dementia 57.1%, terminal cancer 52%	Dementia, cancer	Yes Dementia versus cancer, OR= 0.12 with 95%CI (0.09–0.16)
Messinger-Rapport et al, 2005 (16)	Cross-sectional study	Nursing home N = 177 Mean age: 82 ± 9 Women: 72%	Dementia, depression, number of morbidities	No
Anderson et al, 2006 (15)	Cross-sectional study	Nursing home, peritoneal Dialysis N = 109 Mean age: 62 ± 12.8y Women: 61%	Coronary heart disease, diabetes, stroke, dementia, depression, peripheral vascular diseases, decubitus ulcers	Yes Coronary heart disease, OR= 4.24 with 95%CI (1.49–12.02)
Chen et al, 2007 (14)	Cross-sectional study	Inpatients with acute myocardial infarction, patients with kidney disease N = 4003 Mean age: 73y (55–99y) Women: n = 118 (39%)	Pulmonary disease, heart failure, cancer, coronary heart disease, diabetes, stroke	Yes Stroke, OR=2.65 with 95%CI (1.51–4.65); Heart failure, OR=2.28 with 95%CI (1.43–3.61); Coronary heart disease, OR= 1.74 with 95%CI (1.09–2.789)
Esteve et al, 2009 (3)	Cross-sectional study	Inpatients, older patients, N = 103 Mean age: 86.5± 6.6y Women: n = 65 (72%)	Charlson index score	Yes
Ismail et al, 2010 (13)	Cross-sectional study	Inpatients, burn N = 63	Significant morbidities	Yes

Abbreviations: DNR, do not resuscitate; ICU, intensive care unit; y: year; vs: versus; OR: Odd ratio; CI: Confidence interval; ±: Standard deviation

Figure 2

Forest plots for probability of decision not to resuscitate; (A): cancer; (B): cognitive impairment; (C): heart diseases; (D): stroke. The black box area is proportional to the sample size of each study, and horizontal lines correspond to the 95% confidence interval. White diamond represents the summary value. The dashed line corresponds to an odds ratio of 1.0, equivalent to no association



making (25). Second, multimorbidity" in older patients induce greater health vulnerability, which is independently associated with worse health outcomes regardless of the level of care given (25). Third, older patients with multimorbidity and their families are less likely than younger patients to accept aggressive treatment or care focused on life extension (26).

Our findings also underscored significant associations of DNR orders with specific morbidities, particularly cognitive impairment, cancer and stroke. The probability of DNR orders was 1.15-fold higher in the case of cognitive impairment, which may be explained by the poorer prognosis and poorer quality of life in this population (2, 9). Cancer was also associated with a risk of DNR multiplied by 2.58. This may be related to the poorer survival, cognitive and functional status after cardiopulmonary resuscitation in this specific population (8, 20). The interpretation of the latter result should yet take into account the high heterogeneity between studies (I2=94.3%) explained by the fact that the use of the outcome "cancer" was too vague compared to prognosis factors such as its type or tumor stage (5). Moreover, sub-analyses according to the type of cancer were not pursued due to the limited number of selected studies. Finally, we found that stroke was associated with DNR orders with a significant OR calculated at 1.97. One explanation may rely on the fact that strokes lead to higher rates of in-hospital mortality reaching 9.9% (1, 29), which may facilitate the DNR decision-making. Furthermore, the complications of stroke after resuscitation, particularly the low functional status and the poor quality of life, may explain this result (7). In contrast, our meta-analysis found no significant association between heart diseases and DNR orders. This interesting finding could be explained by the significant therapeutic advances reached in this field among older patients and the ensuing major improvements of the vital and functional prognosis (7, 27, 28). Such improvements may encourage physicians not to stop care and patients with heart diseases to express the desire to be resuscitated (27, 28).

Our systematic review and meta-analysis has some limitations related primarily to the methodology of selected studies. First, most of studies (81.8%) have used a cross-sectional design, which may limit the exploration of the association between morbidities and DNR and precludes any causal inferences. Second, data were retrospectively collected in 59% of the studies, which may affect the quality of recorded data. Third, heterogeneous populations and outcomes made comparisons difficult.

In conclusion, we found that DNR orders were positively associated with multimorbidity. This association depended on the type of morbidities; stroke, cancer and cognitive impairment, but not hearts diseases, being significantly associated with the decision of DNR. Future studies should examine the impact of the entanglement of these morbidities on DNR decision in older adults.

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ERRATUM

Erratum to: The Journal of Nutrition, Health & Aging
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Erratum to: Dyspnea: A Strong Independent Factor for Long-Term Mortality in the Elderly

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The already published version of the article "Dyspnea: A Strong Independent Factor for Long-Term Mortality in the Elderly" contains an error in the authors list. The list of author is: M. Berraho, C. Nejjari, K. El Rhazi, J.F. Tessier, J.F. Dartigues, P. Barberger-Gâteau, C. Raherison