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Clinical paper

Outcomes in adults living with frailty receiving cardiopulmonary resuscitation: A systematic review and meta-analysis

Joseph Hamlyn^a, Charlotte Lowry^a, Thomas A Jackson^{a,b}, Carly Welch^{a,b,*}

Abstract

Background: Frailty is a clinical expression of adverse ageing which could be a valuable predictor of outcomes from cardiac arrest. The aim of this systematic review was to evaluate survival outcomes in adults living with frailty versus adults living without frailty receiving cardiopulmonary resuscitation (CPR) following cardiac arrest.

Methods: A comprehensive search of MEDLINE, EMBASE, CINAHL, and Web of Science databases was performed using pre-defined search terms, with no date or language restrictions applied. Prospective and retrospective observational studies measuring outcomes from CPR in adults assessed for frailty using an accepted clinical definition were selected.

Results: Eight eligible studies were included. Seven retrospective observational studies presenting high methodological quality were included in a meta-analysis comprising 1704 participants. Frailty was strongly associated with an increased likelihood of mortality after CPR, with moderate inter-study heterogeneity (OR = 3.56, 95% CI = 2.74–4.63, $I^2 = 71\%$).

Discussion: This review supports the consideration of frailty status in a holistic approach to CPR. The present findings suggest that frailty status provides valuable prognostic information and could complement other known pre-arrest prognostic factors such as comorbidities in the context of Do Not Attempt CPR consideration. Awareness of the poorer outcomes in those living with frailty could support the identification of individuals less likely to benefit from CPR. Validation of our findings and evaluation of quality-of-life in frail individuals surviving cardiac arrest are prerequisites for the future integration of frailty status into CPR clinical decision-making.

Registration: Prospectively registered on PROSPERO: CRD42020223670.

Keywords: CPR, CFS, Rockwood, Mortality, Advance Care Planning, Futility

Introduction

Frailty defines a state of homeostatic insufficiency in the context of a stressor event, arising from the concurrent deterioration of multiple physiological systems with age.^{1,2} The prevalence of frailty in the community is estimated to be 10.7% in adults aged 65 and over.³ In England, the number of frail older adults acutely admitted to hospital increased more than twofold between 2005 and 2013.⁴ Importantly, the increasing prevalence of frailty with age has been validated across numerous epidemiological studies.^{3–6} In line with ageing population structures it is apparent that the influence of frailty on healthcare provision is expected to grow.

At the moment there is no gold-standard tool for the diagnosis of frailty, and several validated methods of evaluation currently form the forefront of our approach to frailty in clinical practice. National Institute of Health and Clinical Excellence (NICE) guidance recommends the assessment of frailty status using the Clinical Frailty Scale (CFS) in individuals admitted to hospital with COVID-19, where appropriate, as part of a holistic approach to patient care.⁷ More broadly, NICE guidance for the clinical assessment and management of multimorbidity recommends the systematic identification of frailty in individuals presenting with multiple long-term conditions.⁸

Furthermore, in 2017 the NHS introduced a contractual requirement for the systematic identification of patients over the age of 65 living with frailty in a primary care setting.⁹ Our current understanding

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of how frailty status influences outcomes following receipt of CPR for cardiac arrest is limited, however.

We know that CPR is most likely to be effective when cardiac arrest has a reversible cause. Identifying individuals in whom cardiac arrest may be considered an irreversible cause of death, due to severe illness or a significant progressive decline preceding arrest, is therefore an important step for the prevention of futile and traumatic resuscitative attempts. Previous studies show that the likelihood of survival-to-discharge in adults suffering a cardiac arrest generally decreases with age.^{10,11} In isolation, however, older age is not a sufficient criterion to withhold CPR from a patient.¹² Frailty is a clinical expression of adverse ageing which could be a more valuable predictor of outcomes from cardiac arrest. A better knowledge of this could enable identification of which individuals are less likely to benefit from CPR, and inform discussion of a Do Not Attempt CPR (DNACPR) decision.

To date, relevant studies have been primarily small and single-centre, indicating the need for synthesis of the available primary research. The objective of this systematic was to identify all published papers comparing the outcomes in adults living with frailty versus adults living without frailty receiving CPR following cardiac arrest.

Methods

This systematic review was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) – CRD42020223670. It is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.

Search strategy and selection criteria

We searched MEDLINE, EMBASE, CINAHL and Web of Science databases from inception to 26th February 2022, with no language restrictions applied. The search strategy included recognised search terms for prospective and retrospective observational studies, frailty status, and CPR. The reference lists of all identified studies were also screened, in addition to Google Scholar and conference indices, in order to identify any studies missed from database searches or grey literature. All aspects of study screening were performed independently by two assessors (J.H. and C.L.), and disagreements were resolved through discussion. Final arbitration for inclusion was performed by a third reviewer (C.W.). Inclusion criteria applied were: (i) Adults aged 16 years and older suffering from a confirmed cardiac arrest with attempted CPR, (ii) Diagnosis of frailty using an accepted clinical definition, including but not limited to the Fried frailty phenotype, Frailty Index and CFS, and (iii) Comparison of outcomes from CPR to patients not meeting the criteria for frailty using a recognised clinical definition. Prespecified exclusion criteria were: (i) CPR not performed, and (ii) DNACPR decision in place.

Methodological quality

Study risk of bias was evaluated by two independent assessors using the Newcastle-Ottawa-Scale (NOS).¹³ Studies were awarded up to nine points based on assessment against three parameters: selection, comparability, and outcome. The tool was modified so that studies could receive an extra recognition point for the ‘Comparability of cohorts’ section if they adjusted for three predetermined confounders (age, shockable rhythm, comorbidities) important to adjust

for in analysis of outcomes from cardiac arrest. Disagreements were resolved through discussion, and a final decision was made by a third reviewer when no consensus could be reached. Studies were considered to be of ‘high-quality’ if they scored seven or greater. Certainty of evidence at the outcome level was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.¹⁴

Data synthesis

Data was collected in duplicate on study characteristics, patient demographics (age, sex, comorbidities, initial cardiac rhythm) and frailty (status, diagnostic tool used). Outcome data sought included mortality (prespecified as inpatient or 30 days) following receipt of CPR for cardiac arrest. We also aimed to extract data on post-resuscitation quality-of-life were this to be available. All included studies formed part of a narrative synthesis. Studies presenting sufficient data to calculate estimate of effect for mortality were included in meta-analysis. Meta-analysis was performed using RevMan software (version 5.4).¹⁵ The Mantel-Haenszel fixed-effect approach was used to calculate a combined unadjusted odds-ratio with 95% confidence intervals. Our definition of frailty for the odds-ratio was synthesised using the binary cut-off from each study. The I^2 statistic was calculated to estimate the percentage of variability between studies which can be attributed to heterogeneity.

Results

Literature searches yielded 1731 results after duplicate removal. Of these, 1710 articles were excluded after title/abstract screening. The full-texts of 21 articles were assessed for eligibility after reference screening identified two additional studies for possible inclusion. Reasons for study exclusion were the absence of frailty measures ($n = 4$), wrong publication type ($n = 4$), insufficient data ($n = 2$), no comparison of frail versus non-frail individuals ($n = 1$), and CPR not performed ($n = 2$). Overall, eight studies were identified for inclusion in the review (Fig. 1).

Outcomes from cardiac arrest

Eight studies comparing the outcomes in frail versus non-frail individuals receiving CPR for cardiac arrest were included in a narrative synthesis (Table 1).^{16–23} Of these, seven studies presented sufficient data for inclusion in quantitative synthesis. All studies included in meta-analysis were of a retrospective observational design and considered to be of high methodological quality (Table 2). Four studies received additional recognition by adjusting for all three of age, initial rhythm, and comorbidities in their analyses, as per our modified version of the NOS. One study included in narrative synthesis alone presented a moderate methodological quality due to inexplicit description of how frailty status was ascertained, and uncertainties regarding outcome assessment and adequacy of follow-up.²¹ Certainty of evidence was assessed using GRADE for the outcome mortality from CPR. A “low” quality of evidence rating was assigned a priori due to the observational design of studies included in the review, which predisposes to residual confounding. There were no concerns that warranted downgrading of the certainty of evidence (Table 3). Assuming that relative risk and odds ratio are comparable in magnitude, a large pooled estimate of effect (greater than two-fold) warranted a one level upgrade, suggesting a moderate certainty of evidence.

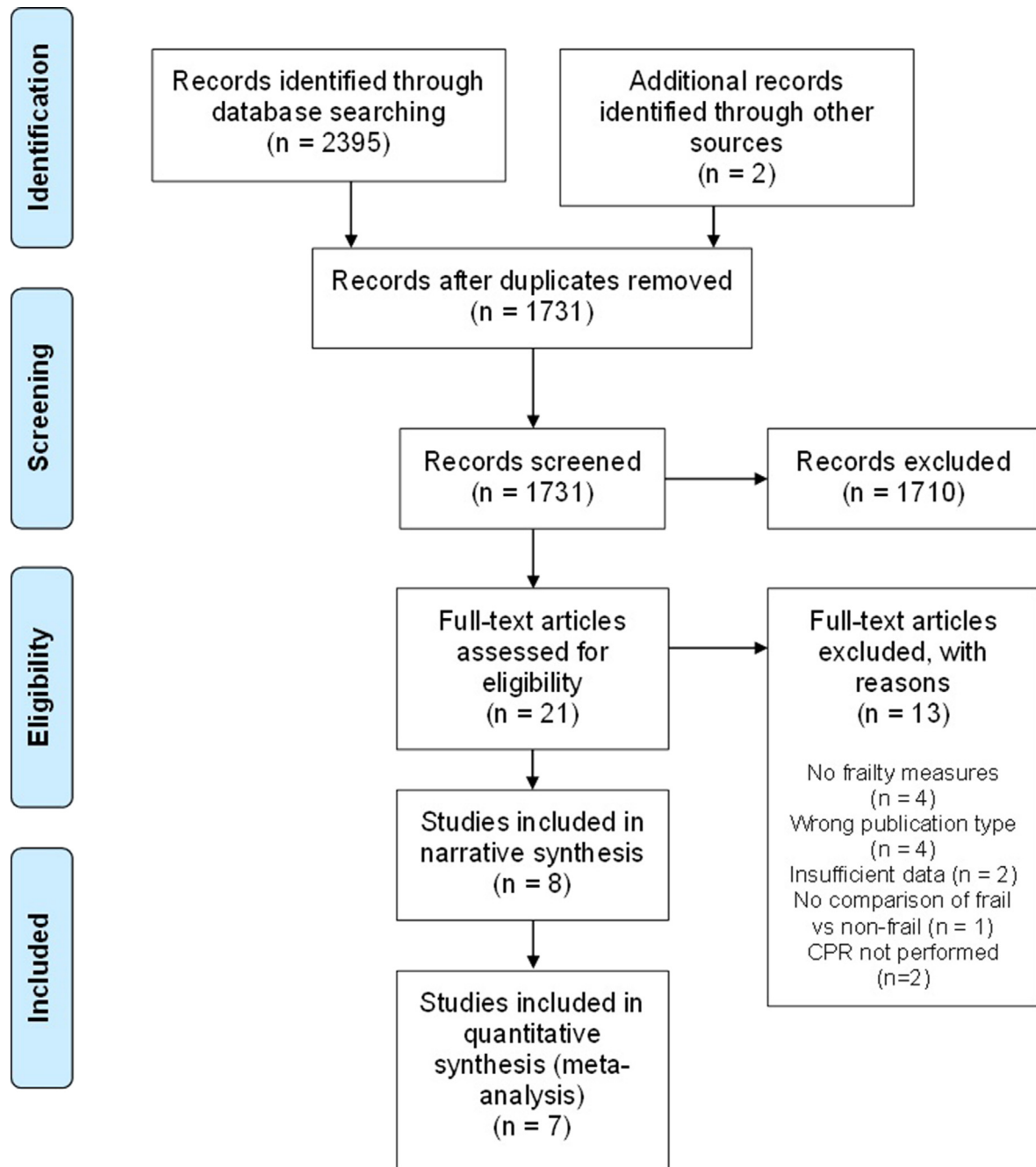


Fig. 1 – Prisma flow diagram exhibiting strategy for study selection, MEDLINE, EMBASE, CINAHL and Web of Science databases were searched from inception to 26th February 2022, with no language restrictions applied. Two additional studies were identified through reference screening of studies initially identified in title and abstract screening. Title and abstract and full-text screening were both performed in duplicate by two independent assessors.

For the purpose of this review, individuals living with frailty are defined as those who met the respective frailty criteria in each individual study. We modified the frailty cut-off score in one study to include a CFS score of four in the non-frail group, consistent with other studies and standard clinical practices.²² Percentage mortality in non-frail participants undergoing CPR was 71.6% compared to 90.2% in frail participants. One study found that no frail patients survived to discharge,¹⁹ while another found only one frail patient survived.¹⁶ A further study showed that after one-year no patient with

a CFS ≥ 6 survived.²³ Three studies analysed for an association between increasing CFS and mortality following receipt of CPR. All three studies demonstrated that greater severity of frailty was associated with reduced odds of survival.^{20,22,23}

The odds of mortality following receipt of CPR in individuals living with frailty compared to non-frail individuals ranged from 1.65 to 29.2 across included studies. The combined unadjusted odds ratio for mortality was 3.56 (95% CI = 2.74–4.63, $I^2 = 71\%$, Fig. 2). Overall, frailty was associated with a statistically significant increased likeli-

Table 1 – Summary of study characteristics. Key characteristics of studies included. The Clinical Frailty Scale (CFS) is a 9-point scale for assessment of fitness and frailty. The Hospital Frailty Risk Score (HFRS) is used to identify frail older adults at risk of adverse outcomes. ROSC = Return of Spontaneous Circulation.

Study, setting	Design	Frailty criteria	Outcomes reported	Inclusion criteria	Exclusion criteria
Wharton, ¹⁶ 2019 District general hospital, UK	Retrospective observational	CFS (≥ 6)	<ul style="list-style-type: none"> Survival to hospital discharge Admission to critical care after ROSC 	<ul style="list-style-type: none"> Adult (>16) IHCA 	<ul style="list-style-type: none"> Non-inpatient arrests Paediatric arrests Cases where CFS cannot be calculated
Fernando, ¹⁷ 2019 The Ottawa Hospital Network, Canada	Retrospective observational	CFS (≥ 5)	<ul style="list-style-type: none"> ROSC In-hospital mortality Discharge location 	<ul style="list-style-type: none"> Adult (≥ 18) IHCA Glasgow Coma Scale of 3 Chest compressions performed 	<ul style="list-style-type: none"> Cardiac arrest in ICU or operating theatre DNACPR decision present Missing data related to baseline function OHCA
Smith, ¹⁸ 2018 Tertiary referral hospital, Australia	Retrospective observational	HFRS (≥ 5)	<ul style="list-style-type: none"> Critical care length of stay following ROSC Hospital length of stay following ROSC Readmission to hospital within 30 days from discharge 	<ul style="list-style-type: none"> IHCA Chest compressions and/or electrical defibrillation performed 	<ul style="list-style-type: none"> Cardiac arrest in persons not admitted to hospital (e.g. visitors, patients in emergency department) Cardiac arrest in subacute units (e.g. palliative care, geriatric medicine)
Ibitoye, ¹⁹ 2020 Tertiary referral hospital, UK	Retrospective observational	CFS (≥ 5)	<ul style="list-style-type: none"> Survival to discharge Discharge location One year survival 	<ul style="list-style-type: none"> IHCA in patients (>60) who received CPR 	<ul style="list-style-type: none"> Repeat cardiac arrests Cases where CPR was discontinued due to presence of DNACPR CFS score non-determinable Non-true cardiac arrest
Xu, ²⁰ 2020 Zigong fourth people's hospital, China	Retrospective observational	CFS (≥ 5)	<ul style="list-style-type: none"> In-hospital mortality 	<ul style="list-style-type: none"> Adult (≥ 18) IHCA 	<ul style="list-style-type: none"> None
Sulzgruber, ²¹ 2016 Out-of-hospital, Austria	Prospective observational	N/A	<ul style="list-style-type: none"> ROSC 30 day survival Favourable cerebral performance category 	<ul style="list-style-type: none"> OHCA with resuscitation attempt by emergency medical service 	<ul style="list-style-type: none"> No professional resuscitation attempt DNACPR decision present
Thomas, ²³ 2021 Tertiary hospital, UK	Retrospective observational	CFS (≥ 5)	<ul style="list-style-type: none"> ROSC 30 day survival Survival to discharge One year survival 	<ul style="list-style-type: none"> Adult (>16) IHCA 	<ul style="list-style-type: none"> DNACPR decision present OHCA
Hu, ²² 2021 Mass General Brigham hospital network, USA	Retrospective observational	CFS (≥ 5)	<ul style="list-style-type: none"> In hospital mortality 	<ul style="list-style-type: none"> Adult (>65) IHCA 	<ul style="list-style-type: none"> Cardiac arrest in emergency department

Table 2 – Risk of bias assessment using a modified Newcastle-Ottawa Scale. Risk of bias was assessed using a modified NOS. The scale was modified by scoring the ‘Comparability of cohorts’ section out of three, rather than two, in order to reflect the presence of three confounders studies should have controlled for in their analyses. The ‘+’ sign indicates studies that were awarded this additional point. The majority of studies had a low risk of bias (overall score ≥ 7). One study presented a moderate risk of bias (overall score 4–6).

Study	Selection				Comparability of cohorts	Outcome			Overall score (/9)
	Exposed cohort	Non-exposed cohort	Exposure ascertainment	Outcome not present at start		Assessment of outcome	Follow-up length	Follow-up adequacy	
Wharton, ¹⁶ 2019	*	*	*	*	**	*	*	*	9
Sulzgruber, ²¹ 2016	*	*	*	*	**	*	*	*	6
Fernando, ¹⁷ 2019	*	*	*	*	***	*	*	*	9+
Smith, ¹⁸ 2018*	*	*	*	*	***	*	*	*	9+
Ibitoye, ¹⁹ 2020	*	*	*	*	***	*	*	*	9+
Xu, ²⁰ 2020	*	*	*	*	***	*	*	*	9+
Thomas, ²³ 2021	*	*	*	*	*	*	*	*	7
Hu, ²² 2021	*	*	*	*	**	*	*	*	8+

Table 3 – GRADE domain certainty of evidence for mortality following receipt of CPR for cardiac arrest. The GRADE framework was applied to assess quality of evidence and risk of bias across studies. Each domain was assigned an a priori ranking of low due to observational study design. There were no serious or very serious concerns. Final quality of evidence was upgraded one level to moderate due to a large effect size (OR > 2).

Mortality from CPR		
GRADE domain	Certainty	Comments
Risk of bias	LOW	Studies generally exhibited low risk of bias as per the NOS.
Inconsistency	LOW	I^2 indicated moderate heterogeneity between studies. However, CIs consistently overlapped across studies, effect estimates were all in same direction and generally of a large magnitude, so no downgrade.
Indirectness	LOW	Study populations in which outcomes from CPR were compared were representative of the review’s population of interest. Outcome reported is imperative for decision-making.
Imprecision	LOW	Number of participants and events sufficient for calculation of precise estimate of effect. Upper and lower limits of CIs indicate frailty is associated with increased likelihood of mortality regardless of where the true effect lies within them.
Publication bias	LOW	Publication bias unlikely. No unpublished results or conference abstracts identified with ‘negative’ findings contrasting to the observed findings in this review.

hood of mortality following receipt of CPR. No studies specifically measured quality-of-life in survivors of cardiac arrest. Two studies included showed that frail individuals were more likely to be discharged to another care facility, rather than home.^{17,18} One study showed that the few frail individuals surviving cardiac arrest following receipt of CPR exhibited poor neurological function.²¹

Discussion

It is recognised that frailty is associated with increased risk of adverse events such as falls and delirium, poorer outcomes from a number of interventions, and reduced functional capacity. This systematic review demonstrates that frailty is a predictor of worse outcomes in patients receiving CPR for cardiac arrest.

Age is often cited as an important predictor of outcomes in patients receiving CPR. The results of this review, however, suggest frailty may be a confounding factor of this relationship. In a previous systematic review investigating out-of-hospital cardiac arrest (OHCA), older age was shown to be an inadequate predictor of outcomes following receipt of CPR.¹² Other factors that are strong predictors of favourable outcomes from cardiac arrest include; whether the presenting rhythm is shockable, if the arrest is witnessed, and if CPR occurs during the daytime.²⁴ These, however, are intra-arrest prognostic factors, and crucial information such as the presenting rhythm are only available once a decision to perform resuscitation has already been made. A requirement for strong pre-arrest prognostic factors is therefore apparent. This review suggests frailty status may provide valuable prognostic information that can be acquired prior to cardiac arrest, and could complement other pre-arrest prog-

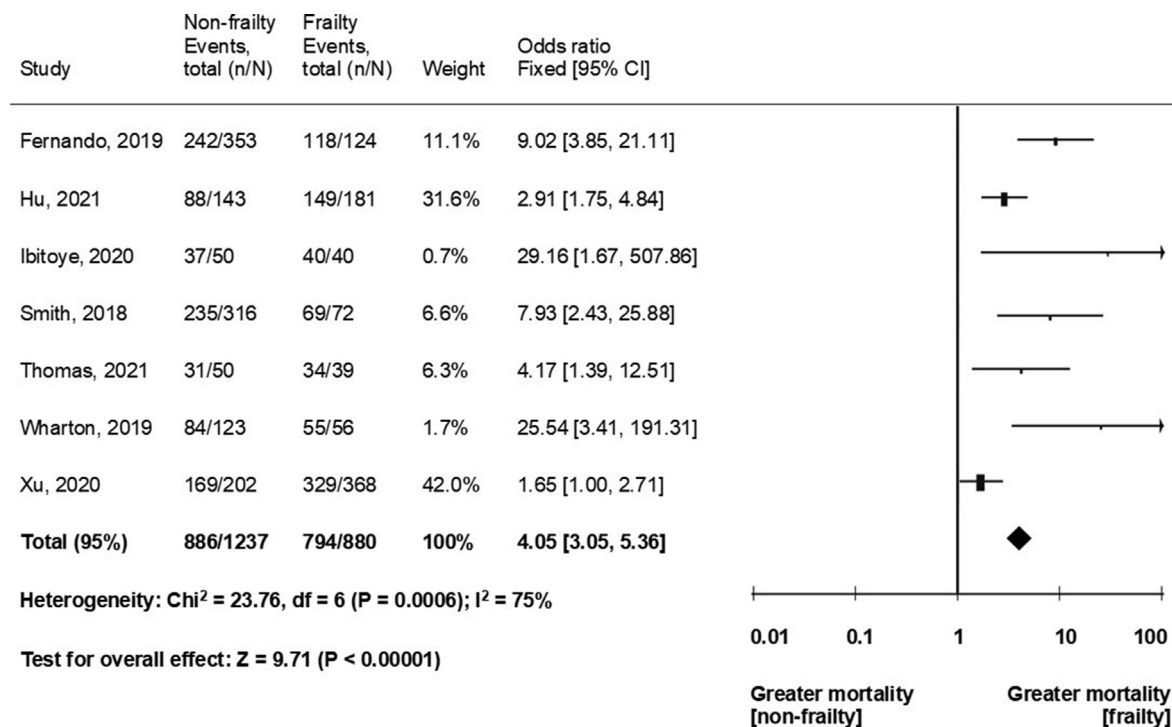


Fig. 2 – Forest plot showing the association of frailty with inpatient mortality, In each study, the timeframe considered was survival to discharge. Individual fixed-effects unadjusted odds ratio are presented with lines indicating 95% CIs and square size proportional to study weight. The black diamond represents the pooled unadjusted odds ratio, whereby the diamond width denotes its 95% CIs.

nostic factors. Previous research has found that older age and specific comorbidities, such as active malignancy and chronic kidney disease, are pre-arrest factors associated with reduced odds of survival from IHCA.²⁴ It is increasingly understood, however, that age and comorbidity interrelate with frailty, and frailty likely better identifies patients vulnerable to adverse outcomes.^{25,26}

The value and practicality of routine frailty measurement has already been demonstrated in acute, surgical, and oncological settings,^{27–30} among others, and thus its further application to support end-of-life decision-making appears both feasible, and of value as indicated by the present findings. Considering frailty cannot be measured at the time of arrest, comprehensive advance care planning with proactive frailty assessment is needed to facilitate this. Concerns regarding the ethical and legal ramifications of a DNACPR decision are a commonly cited barrier to advance care planning, and thus the requirement for validation of our findings and a high-quality evidence base is apparent. This in turn should give clinicians confidence when including frailty status as part of holistic end-of-life decision-making.

In our statistical analysis we used the binary cut-off employed by each respective study to categorise individuals as frail or non-frail, with the exception of one study as previously mentioned. For the CFS a score of five is the most commonly used threshold for frailty.³¹ However, frailty is a spectrum and binary measurement of merely its presence or absence may not be the most effective application of frailty status to DNACPR decision-making. Three included studies found that increasing frailty score was associated with increased odds of mortality following receipt of CPR.^{20,22,23} Across all of these studies survival was markedly reduced in patients with severe frailty (CFS 7–9) compared to individuals living with milder frailty. Ibitoye et

at further found that no frail patients survived CPR, while Wharton et al found that only a single frail patient (CFS 6–9) survived. Clearly, the odds of survival are poor in frail individuals undergoing CPR, and this also raises the question of whether there comes a point of frailty where CPR could be considered futile. Future research should continue to evaluate how the severity of frailty influences outcomes from cardiac arrest, with the aim of more accurately risk stratifying patients regarding their likelihood of survival and favourable post-resuscitation quality-of-life.

Our findings may have particular implications for the consideration of advance DNACPR decisions. Despite significantly lower survival rates in older adults compared to younger adults, research suggests many clinicians hold unrealistically optimistic expectations with respect to outcomes following CPR for cardiac arrest.^{32,33} Equally, older adults often share such misapprehensions regarding their prospects of survival and recovery.^{34–36} It has been shown that many older adults no longer wish to undergo resuscitation after learning the true likelihood of survival.³⁷ Clearly, the true probabilities of survival from CPR are not always reflected by doctor and patient beliefs, raising the concern that many older adults with a small chance of survival are receiving futile resuscitative attempts. Understanding of the poorer outcomes from cardiac arrest in those living with frailty could facilitate a more well-informed shared decision-making process, and may, in turn, permit a dignified and peaceful dying process in a patient who, otherwise, may have undergone futile and traumatic resuscitation. Given the findings of this review, together with an anticipated increase in the number of adults living in older age and with frailty,³⁸ it is conceivable that the present challenges regarding CPR decision-making in adults living with frailty will continue to present on a routine basis.

A systematic review and meta-analysis similar to ours has been recently published.³⁹ This is a rapidly developing field of research, and one clinicians are more acutely aware of since the COVID-19 pandemic. Our review adds two studies newly published in the past year to a comprehensive meta-analysis, and considers the prognostic influence of increasing CFS score where possible. Key strengths of our review include a background of high-quality research methodology across included studies and a meta-analysis presenting a large effect size. The direction of association between frailty and outcomes following receipt of CPR for cardiac arrest was consistent across all included studies. In four studies that performed multivariable analysis, this relationship remained after adjusting for key confounders.^{16,17,19,22} One study found that after controlling for other factors, frailty was associated with a reduced prospect of being discharged home, but not with increased mortality.¹⁸ Confounders such as age, rhythm, and comorbidities were not adjusted for in our meta-analysis, alluding to a key limitation of this review. Considering that adults living with frailty tend to be older and have higher rates of comorbid disease compared to adults living without frailty,^{2,3,5} the present effect size could, therefore, be an overestimation of the effect of frailty on mortality. Indeed, where demographic data was reported, frail participants captured by this review were both older and exhibited greater prevalence of comorbidities, compared to non-frail participants.

In addition to lack of adjustment for confounders in meta-analysis, there were several other notable limitations to our research. Firstly, there was heterogeneity in frailty evaluation tools and numerical thresholds used across included studies, reflecting the current absence of a gold-standard assessment for diagnosis of frailty. Ideally the comprehensive geriatric assessment and CFS should be used in combination, however this is not routinely possible in practice. We suggest that the CFS alone provides an easy and pragmatic tool for frailty assessment and should be used when more comprehensive testing is not feasible. Lack of frailty assessment before the occurrence of OHCA is another recognised problem. In England, older adults are routinely screened for frailty using the electronic frailty index in general practice, and this in turn should prompt consideration of CFS scoring and early discussions regarding advance care planning in primary care. Secondly, we cannot rule out the introduction of bias resulting from retrospective measurement of frailty in knowledge of patient outcomes. Thirdly, our research does not consider the impact of the COVID-19 pandemic. In the wake of the pandemic clinicians appear to be making fewer aged-based decisions and the importance of considering a host of factors as part of a holistic approach to patient care, including frailty, is increasingly recognised. It is clear that the events of the past year have challenged standard approaches to CPR, and we feel it would be of merit to further appraise the impact of frailty status on outcomes from cardiac arrest as we adapt to live with the lasting impacts of the coronavirus. Finally, no included study assessed quality-of-life in frail individuals surviving CPR. Simple outcome measures such as survival alone do not take into account the health and functional deficits survivors may live with, and future studies should address this research gap.

Conclusion

This review shows that adults living with frailty have an increased odds of mortality following receipt of CPR, compared to adults living without frailty. Our findings support the integration of frailty status

into a holistic, multifaceted approach to CPR among other considerations such as age, comorbidities and rhythm, in addition to the patient's wishes. Moving forwards, a large multicentre observational trial is recommended for validation of our results and to address prior discussed limitations. Furthermore, research evaluating the quality-of-life in frail individuals surviving CPR should provide clarity to post-resuscitation expectations, and further facilitate patient decision-making.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No additional acknowledgements.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resplu.2022.100266>.

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