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| **Supplementary Table 1. Representative selection of observational studies of frailty in the ICU.** | | | | | |
| **Reference**  *(First Author, Journal, Year)* | **Design and Population** | **Frailty Instrument, Measurement, and Incidence** | **Outcomes** | **Major Findings** | **Commentary** |
| Hamidi, Am J Surg, 2019 (34) | Retrospective  Evaluated propensity-matched trauma patients (demographics, emergency department physiology, mechanism of injury)  Age ≥ 65  n = 34,854  Admitting Indication:  100% trauma | *Modified FI:*  Fractional index of 11 items drawn from Trauma Quality Improvement Program database.  ≥ 0.27 frail (cutoff determined by Youden index)  50% frail | Primary: in-hospital complications (by organ system)  Secondary: mortality, discharge disposition | Frailty associated with increased rate of complications, hospital mortality; decreased discharge to home. Increasing FI associated with increased rate of complications | Modified FI is primarily a measure of comorbidity with only 1 of 11 elements reflecting functional status; it has been critiqued for this reason. In this study, the cutoff for frailty diagnosis was determined from the data to which it was applied.  This represents a large dataset of older trauma patients that supports the increased risk of a range of adverse outcomes associated with incrementally increased frailty index. |
| Hope, Am J Crit Care, 2019 (57) | Prospective  Only evaluated those admitted through the ED for medical reasons or for complications of non-elective surgery  Age ≥ 50  n = 298  Admitting Indication:  63% medical  19% neurologic  2% surgical  16% other | *CFS:*  Measured by both surrogate and physician researchers not directly involved in care.  1-3 fit  4 vulnerable  5-6 moderate frailty  7-9 severe frailty  Investigator 50% frail  Surrogate 37% frail | Primary: agreement between surrogate and researcher pre-hospital frailty assessment, comparison of validity of surrogate and researcher assessments (by mortality, LOS, and incident disability) | Moderate to substantial agreement between surrogate and researcher scores but with statistically and clinically significant differences. Surrogates less likely to score patients as frail.  Researcher scores more predictive of adverse outcomes (hospital mortality, incident disability). | This study highlights the importance of CFS measurement approach in the interpretation of other studies. Both researcher and surrogate scores predict adverse outcomes but researcher scores perform better overall. |
| Montgomery, Transplantation, 2019 (52) | Retrospective  Evaluation of standardized implementation of frailty assessment in all 17 ICUs in Alberta, Canada  Age ≥ 18  n = 15,238  Admitting Indication:  49% medical  8% neurologic  38% surgical  5% trauma | *CFS:*  Determined by admitting intensivist within 24 hours of ICU admission.  1-4 not frail  5-9 frail  28% frail | Primary: all-cause hospital mortality  Secondary: ICU mortality, hospital discharge disposition, measures of organ support, health service use | APACHE II (22 vs. 17) and SOFA (7 vs. 6) greater in frail patients. Medical/non-operative admissions (69 vs. 57%) more likely for frail patients.  Hospital mortality (23 vs. 9%) greater in frail patients, aOR 1.8.  ICU mortality (12 vs. 7%) greater in frail patients but not when adjusted for covariates.  Vasoactive (57 vs. 24%) and invasive ventilatory (68 vs. 22%) support less often used in frail patients. Non-invasive ventilation (22 vs. 9%) and renal replacement (7 vs. 5%) more often used in frail patients. | This is a reasonable and thorough implementation of CFS in a standardized process including training of medical staff and integration into the electronic medical record system.  The study demonstrates that CFS is associated with mortality in a population of critically ill adults of all ages. The differences observed in the use of various supports requires further study to clarify contributing factors to fully interpret. |
| Fernando, Crit Care Med, 2019 (53) | Retrospective  Only evaluated patients with suspected infection (antibiotics or body fluid cultures)  Age ≥ 65  n = 1,510  Admitting Source of Infection:  48% pulmonary  27% gastrointestinal  14% urinary tract  4% skin/soft tissue  4% nervous system  3% other/unknown | 2 instruments used  *CFS:*  Determined by nursing staff or occupational therapist on ICU admission.  1-4 not frail  5-9 frail  34% frail  *FI-LAB:*  Fractional index of 23 items from ICU admission laboratory values.  < 0.25  mild frailty  0.25-0.40 moderate frailty  > 0.40  severe frailty  65% moderate to severe frailty | Primary: all-cause hospital mortality  Secondary: incident discharge to long-term care, ICU LOS, hospital LOS, hospital readmission within 30 days, resource utilization, hospital costs | Frailty by CFS associated with increased in-hospital mortality (52.1 vs. 29.3%, aOR 1.81 in multivariate assessment).  Frailty by CFS associated with greater resource utilization including days of mechanical ventilation, arterial line usage, renal replacement therapy, transfusion of blood products, and adverse events. Frailty by CFS associated with total costs attributable to laboratory testing, pharmacy, nursing, and non-physician/non-nursing health professionals. Cost per survivor almost double for frail patients ($105,928 vs. $58,505).  FI-LAB moderately correlated (r=0.481) with MODS. | Within this study of older ICU patients with suspected infection, frailty assessed by CFS is associated with increased healthcare utilization and cost.  FI-LAB, a frailty index of laboratory values, may be correlated with adverse outcomes in acute illness. Significant linear correlation with MODS, however, suggests that in the context of the ICU it may not represent premorbid frailty status and instead might reflect the physiologic perturbations of acute illness. |
| Tipping, Phys Ther, 2019 (29) | Prospective  Only evaluated trauma patients  Age ≥ 50  n = 100  Admitting Indication:  100% trauma | 2 instruments used  *CFS*  Determined by trained researchers through chart review and patient/surrogate interview.  1-4 not frail  5-9 frail  13% frail  *Adapted Physical Frailty Phenotype*  Determined through patient/surrogate interview, medical records. Physical elements of original scale adapted as questions.  0-2 not frail  3-5 frail  22% frail | Comparison of two frailty measures: concordance, floor and ceiling effects, construct and predictive validity | Correlation between CFS and frailty phenotype excellent (r=0.77). Cohen kappa moderate (kappa=0.56), weighted kappa good for fit/vulnerable/frail segmentation (kappa=0.72).  Large floor effects observed (CFS 36%, frailty phenotype 57%). No ceiling effects observed (0% and 4%).  Expected correlates of frailty (age, requiring aid to mobilize, falls, hospital admissions, comorbidity) associated with both frailty measures.  Frailty by both CFS and frailty phenotype associated with greater in-hospital mortality. Only frailty phenotype associated with ICU mortality. | Both measures of frailty (CFS and adapted physical frailty phenotype) identified a somewhat lower percentage of patients as frail in this study compared to many other studies in the ICU, likely related to the specific population chosen (relatively younger, trauma patients).  Both measures of frailty appear to be well correlated and often identify similar patients as frail, and they both perform reasonably well with regards to construct and predictive validity with expected nuances to their significance. Both scales display floor effects that reflect a valid focus on degrees of frailty rather than degrees of wellness. |
| Ferrante, Chest, 2018 (25)  Ferrante, Am J Resp Crit Care Med, 2019 (30) | Prospective  Assessment of a longitudinally tracked cohort of geriatric patients who were admitted to an ICU for medical or surgical reasons; initial enrollment included only those non-disabled in four ADLs and community dwelling  Age ≥ 70  n = 303  Admitting ICU:  38% MICU  38% CCU  20% SICU/CTICU  4% other | *Fried Physical Frailty Phenotype*  Evaluation of the original scale including physical tasks at 18 month intervals on an outpatient basis.  0 non-frail  1-2 prefrail  3-5 frail  45% frail | Primary: post-ICU disability count  Secondary: incident nursing home admission, time to death after hospital admission through 6 months of follow up | Frailty relative to non-frailty associated with 41% increase (aRR 1.41 in multivariate assessment) in disability over 6 months following critical illness. Prefrailty associated with 28% increase (aRR 1.28) in disability. Significant interaction with cognitive impairment occurred. Among cognitively impaired patients, disability burden significantly increased for each frailty count (RR 1.54) and was less significant among cognitively intact patients (aRR 1.18).  The rate of incident nursing home admission increased with increasing frailty (not-frail 24%, prefrail 38%, frail 59%; frail to non-frail aOR 3.52, prefrail to non-frail no difference in multivariate).  Mortality from ICU admission through 6 months follow up significantly increased for frail (54%) compared to non-frail (26%) and prefrail (25%) (aHR 2.00 per frailty count). | This is a high-quality longitudinal assessment of a cohort of initially community-dwelling older adults.  Within the study, Fried physical frailty phenotype is associated with an increased post-ICU disability burden that persists through at least 6 months of follow up in addition to an increased likelihood of mortality and incident nursing home admission. |
| Zampieri, Intensive Care Med, 2018 (33) | Retrospective  Assessment of admissions to 93 ICUs in Brazil for any indication.  Age ≥ 16  n = 129,680  Admitting Indication:  29% elective surgical  10% urgent surgical  61% medical | *Modified FI*  Used as absolute count of 11 items drawn from administrative database.  0 non-frail  1-2 prefrail  3-11 frail  19% frail | Primary: in-hospital mortality  Secondary: discharge home without need for nursing care, ICU and hospital LOS, utilization of organ support and transfusion | Frailty associated with increased rate of in-hospital mortality relative to non-frailty (29% vs. 13%, aOR 2.42 in multivariate analysis). A greater association between frailty and mortality was observed in patients with a lower SOFA score.  Frailty associated with decreased rate of discharge to home without nursing support and longer ICU and hospital LOS. | Modified FI is primarily a measure of comorbidity with only 1 of 11 elements reflecting functional status; it has been critiqued for this reason.  This large study demonstrates that the association of frailty with increased in-hospital mortality might be most significant among patients with lower SOFA scores. Frail and non-frail patients had similar mortality rates with high SOFA scores. |
| Shears, J Crit Care, 2018 (59) | Prospective  Assessment of patients admitted to either of two ICUs  Age ≥ 18  n = 150  Admitting Indication:  76% medical  5% neurologic  19% surgical | *CFS*  Assessed by each of a research coordinator (through chart review, patient interview, and proxy interview), an occupational therapist, and a geriatrics resident as feasible.  Full 1-9 scale used without categorical grouping | Primary: reliable as determined by mean difference of CFS scores between pairs of raters  Secondary: in-hospital mortality, ICU and hospital LOS | No statistically significant difference in mean CFS scores observed between raters (research coordinator, occupational therapist, geriatrics resident). There was a statistically significant difference in the research coordinator score obtained by family interview compared to patient interview. No differences were considered clinically important (greatest difference of mean CFS score observed between raters 0.26).  No significant differences observed between frail and non-frail patients in multivariate assessment of secondary outcomes. | This study suggests that CFS can be implemented in the ICU with a range of providers to determine premorbid frailty status. The specific protocols used to achieve such reliable assessments are not readily accessible. |
| Flaatten, Intensive Care Med, 2017 (49) | Prospective  Transnational cohort of consecutive very old patients across 311 European ICUs  Age ≥ 80  n = 5021  Admitting Indication:  42% medical  10% neurologic  18% elective surgery  10% emergency surgery  11% other | *CFS*  Determination of score by ICU staff through patient/proxy interview. Intentionally no training provided for use; scale considered self-evident.  1-3 not frail  4 prefrail  5-9 frail  43% frail | Primary: survival at ICU discharge and 30 days after ICU admission  Secondary: use of ICU procedures, treatment withholding or withdrawal | Significantly decreased ICU and 30-day survival for frail (73%, 59%) compared to prefrail (80%, 71%) and not frail (82%, 76%) patients. Frailty independently associated with mortality in multivariate analysis (aHR 1.54 for frail vs. fit).  Both treatment withholding and withdrawal were observed more frequently in frail (31%, 15%) than in prefrail (21%, 11%) or not frail (14%, 10%) patients. | This study suggests that CFS is associated with mortality among very old intensive care patients. The substantially greater rates of withholding and withdrawal of treatment for frail patients, not factors considered in the multivariate assessment, could potentially contribute to some of the difference in mortality observed between groups. |
| Heyland, Intensive Care Med, 2015 (37) | Prospective  Assessment of a longitudinal cohort of very old intensive care patients admitted to hospitals across Alberta, Canada  Age ≥ 80  n = 610  Admitting Indication:  62% medical  14% elective surgery  24% emergency surgery | *FI-43 (CGA)*  Assessment performed by study personnel, which includes a 43-item index used as a fractional score of the total possible score  <0.2 fit  0.2-0.4 mild frailty  >0.4 severe frailty  59% frail | Primary: physical function by SF-36 Physical Component scores at 3, 6, 9, and 12 months  Secondary: survival at 12 months | Frail compared to fit patients were significantly less likely to recover to within 10 points of their surrogate-established baseline for the SF-36 physical component score at 12 months (aOR 0.32 in multivariate analysis).  Frail compared to fit patients were significantly less likely to survive at 12 months (aOR 0.53 per 0.2 FI). | In a cohort of very old intensive care patients, frailty as determined by the 43-item FI from the comprehensive geriatrics assessment was associated with failure to recover back to a surrogate-determined baseline physical fitness. Frail patients were also significantly less likely to survive through 12 months. |
| Bagshaw, CMAJ, 2014 (51)  Bagshaw, Crit Care Med, 2015 (64) | Prospective  Assessment of ICU patients across 6 hospitals in Alberta, Canada  Age ≥ 50  n = 421  Admitting Indication:  34% surgical  7% cardiac arrest  59% other | *CFS*  Determination of score by trained coordinators through patient and proxy interviews along with chart review.  1-4 not frail  5-9 frail  33% frail | Primary: in-hospital mortality  Secondary: ICU mortality, 6-month mortality, health-related quality of life (SF-12, EQ-5D), ICU treatments, major adverse events, health services utilization, health-related quality of life (EQ-5D and SF-12 Physical and Mental Component) scores at 6 and 12 months | In-hospital mortality significantly increased for frail (32%) compared to not frail patients (16%) (aOR 1.81 in multivariate analysis); mortality at 1 year also significantly increased (48% vs. 25%, aHR 1.82). There was no difference in ICU mortality observed between groups. Limitations of medical therapy were observed more frequently among frail patients than not frail patients (34% vs. 12%).  Among survivors, frailty compared to non-frailty was associated with longer ICU and hospital LOS and with an increased incidence of major adverse events.  Frail compared to not frail survivors were less likely to be living at home independently at discharge, 6 months, and 12 months (31% vs 67%). Among survivors independent at baseline, frail patients were more likely to become functionally dependent (71% vs. 52%). Frail survivors had greater problems across all EQ-5D domains at 6 and 12 months. For the SF-12, frail patients had lower mental component scores at both 6 and 12 months. Frail patients had lower physical component scores at 12 but not 6 months. | Frailty as determined by CFS was associated with increased in-hospital and 1-year mortality but not ICU mortality, as observed in other studies. Frail patients were more likely to have limitations of medical therapy that could contribute to the observed mortality at different time points and locations.  The CFS scale notably references functional disability as an element of frailty, suggesting that caution be taken when interpreting measures of disability, particularly in the context of questions of the reliability of its implementation. With that said, the assessed incidence of new functional dependence was significantly increased among frail compared to not frail survivors in this cohort.  Frail survivors of critical illness were found to have significantly lower scores of health-related quality of life compared to their robust counterparts at 6 and 12 months. The study is consistent with other literature, but it is limited in that it does not establish a relative baseline for either group with which to compare besides the general population of the province. |
| Le Maguet, Intensive Care Med, 2014 (26) | Prospective  Assessment of ICU patients across 4 hospitals in France  Age ≥ 65  n = 196  Admitting Indication:  26% medical  26% scheduled surgery  39% unscheduled surgery  9% trauma | 2 instruments used  *CFS*  Determined through patient/surrogate interview, medical records. Uncertain who assigned the score.  1-4 not frail  5-9 frail  23% frail  *Adapted Physical Frailty Phenotype*  Determined through patient/surrogate interview, medical records. Physical elements of original scale adapted as questions.  0-2 not frail  3-5 frail  41% frail | Primary: ICU, in-hospital, and 6-month mortality  Secondary: ICU and hospital LOS, survivor living situation at 6 months | For CFS, frailty was associated with increased mortality in the ICU, hospital, and at 6 months; hospital and 6-month mortality remained significant in multivariate analysis. For the physical phenotype, frailty was associated only with increased ICU mortality, including in multivariate analysis. Limitation or discontinuation of treatment was significantly greater for frail patients by CFS.  There was no significant difference in ICU or hospital LOS.  CFS and adapted physical frailty were well correlated (R2 = 0.66). | This study included both CFS and an adaptation of the physical frailty phenotype, which were well correlated in this population of older ICU patients.  Within the study, both measures appeared to be associated with several adverse outcomes, but frailty as measured by CFS showed a more significant association with longer term outcomes (i.e. 6-month mortality) and physical frailty was potentially more associated with shorter term outcomes (i.e. ICU mortality). |
| *ICU = intensive care unit; FI = frailty index; CFS = Clinical Frailty Scale; CGA = Comprehensive Geriatric Assessment; aOR = adjusted odds ratio in multivariate analysis; aHR = adjusted hazard ratio in multivariate analysis; aRR = adjusted relative risk in multivariate analysis; LOS = length of stay; APACHE = Acute Physiology and Chronic Health Evaluation score; SOFA = Sequential Organ Failure Assessment score; SF-12 = 12-item Short Form Survey; SF-36 = 36-item Short Form Survey* | | | | | |