The VIP-2 study: Development and validation of a mortality risk score for very old intensive care patients (≥ 80 years):

Study group

Based on the European Society of Intensive Care Medicine (ESICM) network, and Health Care and Research Outcome (HSRO) section (www.esicm.org).

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The study is registered at: https://clinicaltrials.gov/show/NCT03370692

Background

The increased demand for intensive care leaves many physicians with difficult decisions given the shortage of ICU beds in several countries (1). This is particularly true for "Very old Intensive care Patients" (VIP, ≥80 years old) partly because their life expectancy is limited. Are ICU admission and treatment proportional to their chances of survival? Indeed, all European countries are faced with this growing challenge related to these VIPs.

The triage process prior to admitting a VIP to the ICU differs from the less elderly, and should ideally use different tools than in younger patients. At present, we have no ideal combination of independent prognostic factors associated with benefit from intensive care in this group (2). Even within a country there may be different opinions about the triage process. Other variables, apart from age, are important prognostic factors in the critically ill elderly patient, such as pre-existing co-morbidity and acute organ failure. Geriatric syndromes like frailty, sarcopenia, delirium and dementia probably play a major role as well. Frailty has been defined as a clinical state of increased vulnerability from age-associated decline in physiological reserves and function in many physiological systems.

Our group recently conducted and published results from a large European study in this population with an evaluation of frailty as a prognostic factor for outcome (3).

Aims of the study

The two main aims of the study:

1. To investigate the relation of Frailty, Activity of daily life, Cognitive functions and Co-morbidity with survival at 30 days (and 6 months in a sub-study)
2. From the results design a prognostic score that will be validated in this study cohort

Three secondary aims [a]

1. Estimate survival at 6 months and its associated prognostic factors (in a predefined subpopulation of the study)
2. Estimate inter-rater reliability of the Clinical Frailty Score (CFS) (in a subpopulation)
3. To analyze the relation between CFS, Functional and cognitive status

[a]: optional in a subset of ICUs willing to do this extra work

Methods

Description of methods: main study

A prospective cohort study in European ICUs.

Eligible patients: Consecutive acutely admitted elderly patients (≥ 80 years) to an ICU. In some countries informed consent will be necessary.

Exclusion criteria: Elderly patients (VIP's) admitted to the ICU after planned surgery.

Recruitment period: 6 months or first 20 patients.

Study variables: See also CRF in the end

- Age [continuous]
- Gender [f/m]
- Indication for ICU admission [See list in appendix with 11 admission categories]
- Habitat before the index hospital admission [Home without help; home with support; living with family; nursing home; other hospital]
- Scores at admission
    1. Clinical Frailty Scale (CFS) [continuous]
    2. Activity of daily life score (Katz) [continuous]
    3. Cognitive function (IQCODE) [continuous]
    4. Co-morbidity (Comorbidity Polypharmacy Score: CPS) [continuous]
    5. SOFA score (Individual values for each of the 6-organ system) [categorical 0/1/2/3/4 for each of the 6 components]
- Common ICU procedures
    - Invasive Mechanical ventilation (with start date, duration) [y/n; duration]
    - Vasoactive drugs (NE or E, vasopressin, dopamine is excluded [y/n]
    - Renal replacement therapy (with start date and duration) [y/n]
    - Non-invasive ventilation (with start date and duration) [y/n]
    - Tracheostomy perfomed [y/n]
- ICU length of stay (hours)
- Hospital length of stay (days)
- Limitation of care (withhold and withdraw), and day after admission with such decision
    - Withhold [y/n; days since admission]
    - Withdraw [y/n; days since admission]
- Vital status at 30 days (alive or dead) [y/n; survivaltime since ICU admission]

Description of methods: sub-study A

A preselected number of ICUs will, for their first 10 patients, study the interrater variability of the Clinical Frailty Scale (CFS). This will be done at admission, when the caregivers of the patient give information about their next-of-kin. One physician and one nurse will simultaneously have conversation with the care-givers, and afterward they give their CFS score independent of each other. This will be used to study the interrater variability of the CFS (see statistics section below). In the main study the worst value will be used.

Description of methods: sub-study B

A preselected number of countries, where follow up of patients after hospital discharge is easy, will record vital status of the VIP at 6 months after admission and the number of days alive after admission if the patients appears to be deceased at 6 months after admission. This information will be used for Kaplan Meier analysis of long-term survival in the cohort and in subgroups.

Statistical analysis:

Normally distributed continuous data will be described as means with 95% CI, and non-normal distributed data as median with 25 to 75 percentiles. Continuous variables will be compared between groups using Mann-Whitney U test, and categorical variables using the Chi-square test or Fisher test as appropriate. SPSS (IBM SPSS statistics, version 24) will be used.
Kaplan-Meier estimate and log-rank test will be used in univariate analysis of 30-days and 6-months survival, multivariate analysis will use Cox regression modelling. These analysis will performed using R (R Foundation for Statistical Computing, Vienna, Austria)

Creation of a prognostic score based on survival analysis (Cox) or binary outcome analysis (logistic regression). We will divide the sample cohort in a development cohort and a validation cohort. The number of events (see below) must be sufficient in both samples. For validation we will use K-fold cross validation and external validation will use a geographically pre-defined subset of ICUs.

Sample size and feasibility

In order to be able to fit a model, the general rule is that 10 events are required per degree of freedom tested. Variables considered to enter the model are gender, location before admission, admission type, age, CFS, ADL, IQCODE, CPS and SOFA score, and some effect might be non-linear thus 480 events are required to develop the model. In the VIP1 study, 30-days mortality of acutely admitted patients was of 38%, based on this number we can estimate the number of subjects included in the development set should be 1300. Hypothesising a 10% drop-out, the number of subject in the development set should be 1400.
In the VIP1 study, 4100 acutely admitted patients were included from 311 ICUs. Between 250 and 310 ICUs are expected to participate in the VIP2 study, hypothesising the recruitment rate will be the same than in the VIP1 study, we may expect between 3300 and 4100 patients to be included.

Data security and storage

Data security in the VIP2 study follows industry standards. The data entry forms and database are run on a secured server and are composed of a MySQL database and PHP web-application. Data is secured with Secure Socket Layer (SSL) encryption when transported into the database and data is stored on servers located on the campus of Aarhus University, Aarhus C, Denmark. The servers are maintained and managed in a professional server environment in co-operation between the IT Department and the Department of Clinical Medicine. The server rooms have physical access control and logging of personnel access. Other security measures include hardware and software firewalls. For technical inquiries please contact the data-manager: Jesper Fjølner, MD. email: contact@vip2study.com.

Ethical considerations

This study is a prospective non-interventional study with a central registration of prospective defined variables. As such the study must undergo ethical clearance at each national level according to national/local rules and

guidelines. For those countries where patient consent is required, an information leaflet in the national language will be developed to describe the study and ask for participation, either from patient or next-of-kin. A template in English is designed and available.

A problem is of course that most of these elderly patients with an acute ICU admission often are in a severe condition with limited abilty to give any consent, and a significant number, probably up to 40%, will not survive 30 days. Hence a substitute for informed consent from the patient him/herself will be necessary for participation in the study if such consent is required.

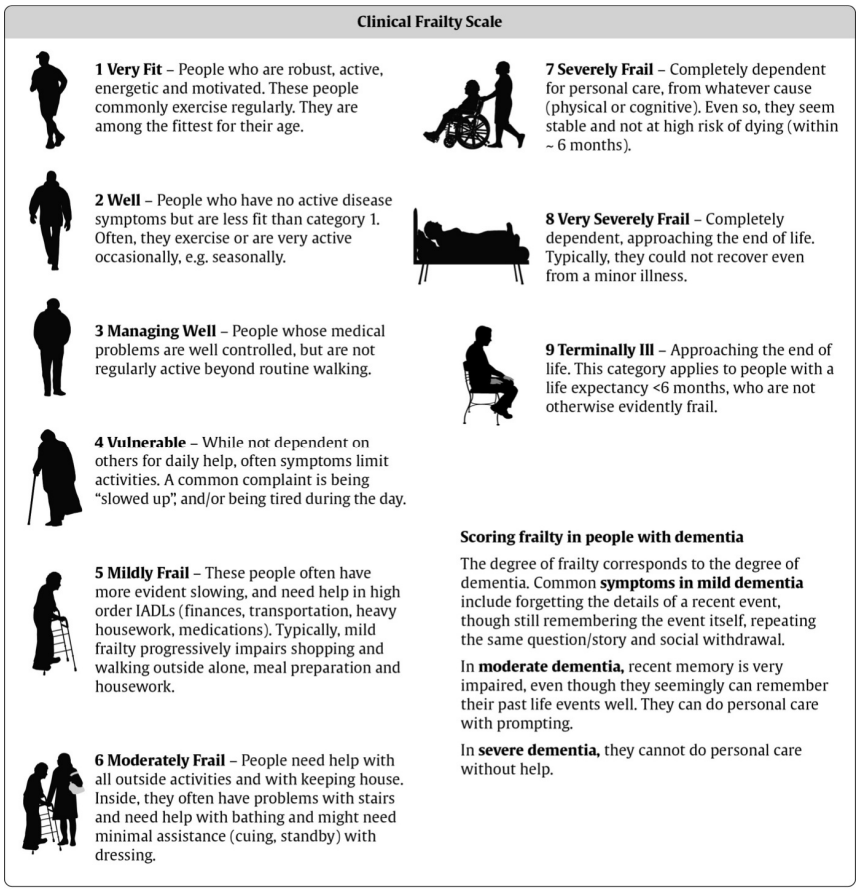
Scores, questionaires and lists

List of admission categories:

1. Respiratory failure
2. Circulatory failure
3. Combined (1&2)
4. Sepsis (according to sepsis 3)
5. Multi-trauma without head injury
6. Multi-trauma with head inury
7. Isolated head injury
8. Intoxication
9. Non-trauma CNS causes
10. Emergency surgery
11. Other causes

Clinical Frailty **Scale (3)**

As used in the VIP1 study, a score from 1-9 will be recorded



Activity of daily life index (KATZ ADL) (4)

A score from 0 to 6 will be recorded

KATZ INDEX OF INDEPENDENCE IN ACTIVITIES OF DAILY LIVING*

Activities *POINTS (1 OR 0)*	***Independence*** *(1 POINT)* ***NO*** *supervision, direction, or personal assistance*	***Dependence*** *(0 POINT)* ***WITH*** *supervision, direction, personal assistance, or total care*
BATHING Points: _____	(1 point) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area, or disabled extremity.	(0 points) Needs help with bathing more than one part of the body, getting in or out of bathtub or shower. Requires total bathing.
DRESSING Points: _____	(1 point) Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	(0 points) Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	(1 point) Goes to toilet, gets on and off, arranges clothes, and cleans genital area without help.	(0 points) Needs help transferring to the toilet, cleaning self, or uses bedpan or commode.
TRANSFERRING Points: _____	(1 point) Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	(0 points) Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	(1 point) Exercises complete self-control over urination and defecation.	(0 points) Is partially or totally incontinent of bowel or bladder.
FEEDING Points: _____	(1 point) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 points) Needs partial or total help with feeding or requires parenteral feeding.
TOTAL POINTS: _____	*6 = High (client independent)*	*0 = Low (client very dependent)*

** Slightly adapted with permission from Gerontological Society of America. Katz, S., Down, T.D., Cash, H.R., et al. (1970). Progress in the development of the index of ADL.* The Gerontologist, 10, *20-30.*

Cognitive decline questionnaire (IQCODE)(5)

(see below or web: https://patient.info/doctor/informant-questionnaire-on-cognitive-decline-in-the-elderly-iqcode

Each question is assigned from 1 to 5 points. An average of 3 points/question is normal = no change from 10 years ago.

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) **Short Form**	
Compared with 10 years ago how is this person at:	
1. Remembering things about family and friends - eg, occupations, birthdays, addresses?	A bit worse
2. Remembering things that have happened recently?	Not much change
3. Recalling conversations a few days later?	Not much change
4. Remembering his/her address and telephone number?	Not much change
5. Remembering what day and month it is?	Not much change
6. Remembering where things are usually kept?	Not much change
7. Remembering where to find things which have been put in a different place from usual?	Not much change
8. Knowing how to work familiar machines around the house?	Not much change
9. Learning to use a new gadget or machine around the house?	Not much change
10. Learning new things in general?	Not much change
11. Following a story in a book or on TV?	Not much change
12. Making decisions on everyday matters?	Not much change
13. Handling money for shopping?	Not much change
14. Handling financial matters - eg, the pension, dealing with the bank?	Not much change
15. Handling other everyday arithmetic problems - eg, knowing how much food to buy, knowing how long between visits from family or friends?	Not much change
16. Using his/her intelligence to understand what's going on and to reason things through?	Not much change
Calculate Reset Average score per question =	

Co-morbidity and Polypharmacy score (CPS) (6)

In this score, the number of chronic conditions and the number of different medications taken daily will sum up the score. The number can be from 0 (no co-morbid condition, no medication) to infinity, although in most patients the number will remain < 20. The score can be put into four groups:

- Minor: 0-7 points
- Moderate: 8-14 point
- Severe: ≥ 15 points

SOFA score (7)

A score form 0-24 will be given according to the severity of organ dysfunction in each vital organ system (Circulation, Respiration, CNS, Renal, Coagulation and Liver function)

Table 1. The Sequential Organ Failure Assessment (SOFA) Score*

	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory Pao_2/FIO_2, mm Hg	>400	≤400	≤300	≤200†	≤100†
Coagulation Platelets $\times 10^3/\mu L$‡	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL‡	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d‖	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and FIO_2, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).
‖To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

References

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7. Vincent JL, Moreno R, Takala J, Willatts S, de Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Int Care Med 1996; 22:. pp. 707–10.

Preliminary e-CRF

CORE DATA

Item	Short description
ICU name (automatic)	Short name of the ICU or ICU number
Patient number (automatic)	Consecutive patient number
Reason for ICU admission	Revised list used in VIP1 except planned admission (11 reasons)
Age	At admission, whole number
Gender	Male/Female
Habitat before hospital admission	Choices from a list (5 levels)
Admission SOFA score	Individual scores for each of the 6 dimensions
Clinical Frailty Scale	At admission: values prior to this hospital admission
IQCODE	Mean score of questions answered (up to 16):
Katz ADL index	Sum score (0-6)
CPS	A number from 0 to ≥ 20
Intubation and ventilation	Yes/No, start day after admission and sum of days
Vasoactive drugs	Yes/No
RRT	Yes/No
NIV	Yes/No
Tracheostomy	Yes/no
LOS in the ICU	Sum of hours
LOS hospital	Days
Day of death after ICU admission	Number from 0-30
Withholding life sustaining care	Yes/no Days since ICU admittance
Withdrawal life sustaining care	Yes/no Days since ICU admittance

ADDITIONAL DATA for some predefined ICUs

CSF reliability test:

CFS score assessor 1	Score number
Assessors profession 1	ICU nurse, ICU physician, Dedicated research staff, Other
CFS score assessor 2	Score number
Assessor profession 2	ICU nurse, ICU physician, Other
Information from	Patient, family/caregivers, hospital records, other

Long term survival

Vital status at 6 months	Alive/dead
Day of death after ICU admission	From 0-180
How was survival assessed	Data from registry/hospital files, telephone, GP, national statistics registry, municipal personal records database