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Ageing Population

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Lessons From the "Very Old Intensive Care Patients" (VIP) Project

An overview of the VIP project that studies a subgroup of patients ≥ 80 years, the oldest old, since both ICU mortality and morbidity are increased with advanced age.

During the last 10 years, we have observed an increased interest in research into our oldest intensive care patients. This is brought forward with the expectation of a two-fold increase in citizens ≥ 80 years towards 2050 **(Figure 1)**.

"Old" is an ambiguous term with no clear definitions. Hence the age ≥ 65 years is still used by WHO. This threshold for old is not useful for most European ICUs because the median age of our patients is 65 years or above. For this reason, many perceive a particular need to study a subgroup: patients ≥ 80 years, the oldest old, since both ICU mortality and morbidity are increased with advanced age. This, together with the perceived increase in the European population, is the reason our group has targeted to study ICU patients ≥ 80 years. A research network in Canada (Heyland 2015) started early on with a national multicentre group exploring different aspects of outcomes in critically ill elderly (McDermid 2011) and has performed important studies on the topic. Initially, there was some interest for this topic in Europe, mainly in France, the Netherlands and in the Scandinavian countries, but no formal cooperation across borders existed.

Within the European Society of Intensive Care Medicine, the Health Service Research and Outcome (HRSO) section we had discussions during 2015/16 in order to establish a multinational research programme in Europe, which was called the VIP project. Core members from the section with other international researchers published in 2017 a research agenda in the very old **(Table 1)** and the first large prospective multinational European study was planned, the VIP1 study (Flaatten 2017).

The aim of the VIP project is simply to contribute to new knowledge about the very old (≥80 years) ICU patients, in particular to reveal important factors for survival and post ICU quality of life. Up to that time there were several studies on the topic, but most were retrospective, and often single-centre and with a small number of patients. The VIP project used active national coordinators who were able to gather interest from many ICUs in their countries. This resulted in hundreds of active sites across Europe. Many of these sites and countries remained interested and continued to participate in the VIP network. We achieved a very good response from the intensive care community for the initial VIP-study. Obviously, many ICUs regarded the issue with very old ICU patients as important. All were willing to contribute in prospective studies, even without any funding. One of the most important success factors was the development of an easy-to-use website and web-based electronic case report form (eCRF) that prevented time-consuming data-entry. This website annex eCRF has been used for all three VIP studies performed since 2017 (www.vipstudy.org)

The VIP network has so far conducted three large prospective observational studies **(Table 2)**.

The VIP-1 Study

The main purpose of the VIP-1 study was to study the relation between pre-morbid conditions, like frailty and age, in combination with other markers of severity like the sequential organ failure assessment (SOFA) score, on ICU and 30 days outcomes. Frailty was measured

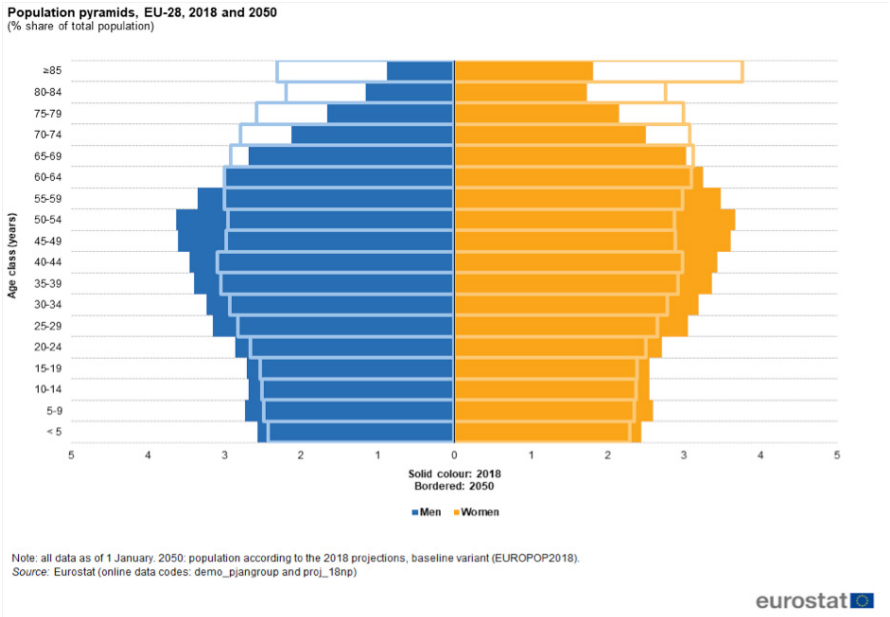

Figure 1. 2050 population according to the 2018 projections. Source: Eurostat.

Important research question	Topic covered
Frailty, sarcopenia, ADL and cognition pre and post ICU admission	Good
Opinions among octogenarians about ICU admission in the very old	Poor
Effects of including a geriatrician pre-and post ICU care	Poor
Effects of non-pharmacological approach to delirium	Poor
Burden of intensive care among caregivers	Some
Prognostic tools	Some
Sepsis	Some
Pharmacokinetics of sedatives	Poor
Trajectories after End of Life decisions	Some

Table 1. Proposed research agenda in the very old ICU patients and how the topics are covered in the research by end 2020. There are still many unanswered questions as can be seen.

Study	Patients	Countries	Sites	Published	ICU patients	Age
VIP-1	5021	21	311	2017	All admission ≥ 80y	≥80
VIP-2	3920	22	242	2019	Only acute admissions	≥80
CoVIP	1474[a]	38	268	Not yet	Only COVID-19	≥70

Table 2. All VIP Studies
[a] on August 2. 2020

using the Clinical Frailty Scale (CFS). We found a near linear relationship between increasing frailty and 30-day mortality **(Figure 2)**. Also, in regression analysis we found frailty to be the better predictor of mortality, even when compared with SOFA score for 30-day mortality.

We, as expected, found huge differences in outcomes between acute and planned ICU admissions in the very old ICU patients, and a sub-study comparing these two groups has been described in more detail (Jung 2019). For this reason, we decided to limit our studies to emergency ICU admission for the coming studies, since we are confident that this is the major challenge concerning the elderly ICU patients.

The VIP-2 Study

The VIP-2 study (Guidet 2020) was launched in 2018 and recruited nearly 4000 patients during a 6-month-period. Having experienced the huge differences between acute and planned admissions the VIP-2 study focussed only on emergency ICU admissions. The main purpose was to study relations between several common geriatric syndromes: cognitive decline, Activity of daily life (ADL), comorbidity/polypharmacy and frailty. For cognitive decline we used the IQCODE questionnaire, which is developed to be answered by close proxies or relatives. Again, we found that frailty, measured with the CFS, was more strongly associated with a poor outcome than the other four geriatric syndromes. A multivariate analysis including all geriatric parameters did not perform better than the model with CFS only. Of note is that the comorbidity/polypharmacy score surprisingly had no discrimination at all between survivors and non-survivors. This emphasises that frailty is not equivalent to the number nor the severity of comorbidities.

The COVIP Study

When we were planning the VIP-3 study the world was hit hard by coronavirus disease. China and Italy were hit first but we anticipated a rapid spread across many European countries. Having a network of very enthusiastic ICUs enabled us to swiftly change plans and start a specific COVID-19 study. We adapted the VIP-1 and VIP-2 study protocols and customised it to fit our knowledge-gaps on COVID-19 in elderly. At that time, many countries were developing treatment and admission protocols and were struggling with survival chances, particu-

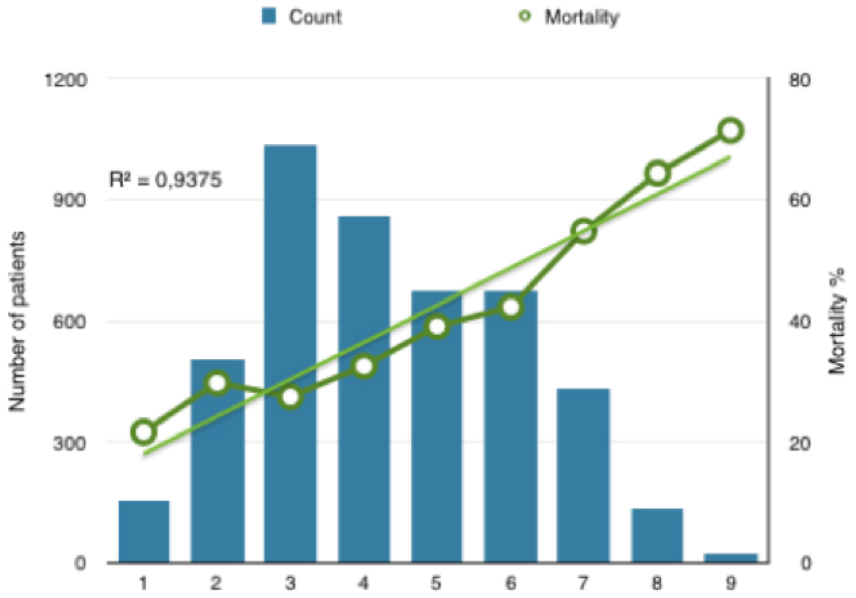

Figure 2. Clinical Frailty Scale

Study	Patients	CFS (median)	CFS >4	SOFA median	LOS	Age (median)	30 d survival
VIP-1	5021	4	44%	4 and 7[a]	1.2 and 2.8[a]	84	93.2% and 62%[a]
VIP-2	3920	4	40%	6	3.9	84	61.1%

Table 3: Comparison of key-variables in VIP-1 and VIP-2.
[a] in planned versus emergency admission

larly for the oldest ICU patients. The CoVIP study (very old COVID-19 ICU patients), started recruitment in March 2020 as the pandemic peaked in Europe. Originally, we planned to study only patients ≥ 80, but since a lot of countries simply did not admit these groups to the hospital nor to the ICU, we decreased the age to patients ≥ 70 years admitted to the ICU.

Our main research question was to describe important predictors for outcomes in a group of elderly patients admitted to the ICU with proven COVID-19. For this study a more detailed eCRF was developed. New end points were a 3 months follow-up with regard to survival and quality of life. The first parts of the study have been completed although the study still includes new patients when a second wave of COVID-19 emerges. We expect to publish the first results from this study towards the end of 2020.

A number of sub-studies from the VIP project has been published **(Table 4)** including individual country data (Germany, Poland, Greece, Norway), and data from the merged databases from VIP-1 and 2. **Table 4** shows some of the most important sub-studies.

Barriers for Observational Studies in Europe

Funding is a problem in cross-country epidemiological studies. It has not been easy to establish funding for such multinational studies in Europe outside the Horizon 2020. Within this system little focus has been on the critical ill elderly patients, although our estimate is that around 500,000 very old patients are treated in European intensive care units each year. Some of the participating countries have managed to receive funding, but only for their country sites and mainly for development and maintaining a database. At the moment our study group is seeking support of the European Society of Intensive Care Medicine (ESICM) as well as the European Geriatric Medicine Society (EuGMS) in order to create both a scientific cooperation but also to make the critically ill patients even more visible, and to launch joint approach to EU funding.

Another important problem we encountered in the VIP-2 study is the rather strict interpretation of the EU data protection directive (GDPR) in most European countries. This directive was implemented while we were starting up and still recruited participating units. In our first study (the VIP-1), most medical ethical boards in most countries allowed us to recruit patients without upfront written informed consent. As this was just an observational study with no interventions written informed consent was deemed not possible and violation of ethical rights was considered minimal as no patient identifying variables were collected. In some countries, we had to inform ICU survivors that their information had been included in the study and could then in retrospect withdraw from participation. This approach has obvious advantages that we can include patients in all stages of disease, also those unconscious at admission and those that later died.

However, this changed with the implementation of the GDPR in Europe. Now, almost all countries insisted on written informed consent by patient or proxy. This had major implications for recruitment to the study. In many countries, the sickest patients seemed to slip through and were not included in the study. We are now in the process of analysing this in two cohorts: one where informed consent was waived, and one where it was considered mandatory. Our concern is that this obviously may be

Study	Patients	Clinical findings
Withholding or withdrawing of life sustaining therapy (Guidet 2018)	1356 from the VIP1 study	Limitations implemented in 27.2% (12.2% withdrawal) with large variations in Europe
Cumulative Prognostic Score Predicting Mortality in Patients Older Than 80 Years Admitted to the ICU (deLange 2019)	3720 patients from the VIP1 study	The model developed had an AUC of 0.8
A comparison of very old patients admitted to intensive care unit after acute versus elective surgery or intervention (Jung 2019)	1324 patients from VIP1 admitted after acute or planned surgery	30 days mortality twice as high in acute surgical ICU admissions vs elective surgery in a matched pair cohort study
Sepsis at ICU admission does not decrease 30-day survival in very old patients: a post-hoc analysis of the VIP1 multinational cohort study (Ibarz 2020)	493 patients from the VIP1 study with sepsis at admission	We found similar 30-day mortality in patients admitted with sepsis compared with other admission categories
Huge variation in obtaining ethical permission for a non-interventional observational study in Europe (deLange 2019)	A survey in 16 country coordinators for the VIP1 study	The time to receive ethical approval for the identical protocol varied from 7 to 300 days. In 9/16 countries informed consent at admission was not required.

Table 4: VIP sub-studies

an important confounding factor of a prospective pure observation study and may have implications for understanding vital epidemiology in critically ill patients. The GDPR will lead to biased results with an overestimation of the "better outcomes" as only the better or surviving patients can provide written informed consent. Of interest, this is of course not confined only to our studies, but all observation studies in critically ill patients when informed consent is not straight forward.

Future Perspectives

At the moment, our group is conducting a study of the elderly COVID-19 patients, but we are also planning a new multinational VIP study. Several options have been discussed, but most probably, we will study the use of a time limited trial (TLT) in the very old patients (Shrime 2016). In patients with uncertain prognosis it can be particularly difficult to decide whether or not to admit a patient to the ICU. In such circumstances, it can be an option to offer an "ICU-trial of limited time" to see if the patient responds to treatment with improvement of vital functions. This trial should be discussed with the patient (if possible) and/or next-of-kin so this is understood and communicated at admission. If condition deteriorates and there is no sign of response to treatment, the patient may then be given comfort and care with withholding or withdrawing vital organ support as the option. At present, we know very little about how often TLT is used in Europe, and even less about in which patients a TLT is used. The data from this exploratory study will be used in planning a controlled trial if possible.

The VIP-network of very active and enthusiastic ICUs across Europe might also enable us to switch to real-time data collection which can be of use for vigilance purposes. Elderly patients often represent the most vulnerable patient population and they are often more severely ill. This means that an unexpected increase of elderly patients in ICUs across Europe with a particular disease might be the first sign of a pandemic or chemical exposure. Development of such sentinel networks needs support from national governments and European Union legislation.

Conflict of Interest

None. ■

Key Points

- The aim of the VIP project is to contribute to new knowledge about the very old (>80 years) ICU patients, in particular to reveal important factors for survival and post ICU quality of life.
- The VIP network has so far conducted three large prospective observational studies.
- The main purpose of the VIP-1 study was to study the relation between pre-morbid conditions, like frailty and age.
- The VIP-2 study focussed only on emergency ICU admissions.
- When we were planning the VIP-3 study the world was hit hard by coronavirus disease.
- We adapted the VIP-1 and VIP-2 study protocols and customised it to fit our knowledge-gaps on COVID-19 in elderly.

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