BMJ Open

Comparison of conservative and invasive approaches on one-year survival among critically ill elderly medical patients: nationwide observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089835
Article Type:	Original research
Date Submitted by the Author:	10-Jun-2024
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Keywords:	PALLIATIVE CARE, Triage, Person-Centered Care, Caregivers, INTENSIVE & CRITICAL CARE, Health Services for the Aged

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Original Research

Comparison of conservative and invasive approaches on one-year survival among critically ill elderly medical patients: nationwide observational study

(The OCTO-REVERSE Study)

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Manuscript word count: 2789

WHAT IS ALREADY KNOWN ON THIS TOPIC:

- The proportion of older patients in intensive care units (ICUs) has been progressively increasing, while the benefit remains unclear across numerous studies exploring this topic.
- The variability in patient selection (ranging from ages 65 to 90, with or without surgery, involving invasive procedures or not) and in outcome measures (assessing mortality or functional status, with early or delayed assessments) has impeded the establishment of a clear consensus, while clinical judgment approximates the one-year survival rate for medical ICU patients over 80 to be around 50%.
- This ensuing absolute uncertainty coupled with an over-optimistic trend for prognosis prediction has paved the way for increasingly invasive strategies, including time-limited trials which a part turn out to be disproportionate.

WHAT THIS STUDY ADDS:

- This long-term real-world comprehensive cohort study demonstrated that the routine care of elderly medical ICU patients is associated with different trajectories depending on whether the approach is invasive or conservative.
- The increased risk associated with the invasive approach is partly explained by the severity of the patients, yet significantly persists after propensity score weighting, and it seems unlikely that a broader application of invasive procedures would have any significant impact on mortality
- The high one-year mortality rate in the invasive group (72%) even questions the opportunity of improving prognosis with a less invasive approach in this frail population, but further studies are needed.

ABSTRACT

Objective: To determine whether an invasive approach is associated with favourable long-term outcomes among elderly medical patients in the ICU, compared to a weighted conservative approach.

Design: Nationwide observational study using data prospectively collected in the National French Healthcare Database (covering 99% of the population, 66 million people).

Setting: Comprehensive multicenter study through the linkage of large-scale national registries (including all public or private facilities) from 2013 to 2018 to avoid ambiguities related to the COVID-19 pandemic

Participants: All nonsurgical patients aged 80 years or older admitted to an ICU in France during the period (n=107 014 patients at 822 hospitals)

Main Outcome Measures: The primary outcome was the one-year survival rate. The association of the two approaches with one-year survival was estimated using a time-dependent Cox model and a propensity score adapted to time-to-event analysis, yielding the average treatment effect in the treated (ATT) and extended weighted Kaplan Meier curves.

Results: 107 014 patients were categorized into two groups based on the type of care received: invasive (n=51 680 [48%] received invasive ventilation and/or vasopressor support) or conservative (n=55 334 [52%] received neither). One-year survival rate was significantly lower in the invasive group than in the conservative group (27% vs 59% estimated with extended time-dependent Kaplan Meier method). The risk of death in the invasive group remained significantly higher after time-dependent propensity score (PS) weighting (hazard ratio, 1.64; 95% CI, 1.60-1.69, p<0.001). The loss

in restricted mean survival time (RMST) was 67.7 days (95% CI, 65.7-69.8) in this group and 31% of deaths occurred the day of initiation of the procedure, or the following day.

Conclusion: Among the whole population of critically ill elderly medical patients in France, the invasive approach was unknowingly associated with end-of-life care in nearly three-quarters of cases. Further research is needed to align intensive care with compassionate goals.

INTRODUCTION

The proportion of older patients in the ICU has been steadily increasing over the past two decades, although the overall benefit remains unclear.[1] Additional research is needed to address the care consequences of this growing population. However, a randomized trial has been deemed infeasible on ethical grounds.[2] The ensuing uncertainty may have led to a decision-making process based solely on clinical judgment, while triage-systems based on even limited evidence would have been preferable.[3] Previous studies on this issue[4–6] have identified older age (≥80 years),[7] non-operative condition,[8] and exposure to invasive procedures[9–11] as prognostic factors that should be considered especially as to long-term outcomes. By conducting a nationwide study that combines these three factors, we aimed to assess the characteristics, management, and long-term outcomes of the entire target population of elderly patients admitted to the ICU for medical reasons in France.

METHODS

STUDY DESIGN AND DATA SOURCES

We performed a nationwide retrospective analysis using data prospectively collected in the Système National des Données de Santé (SNDS), the national French healthcare database that covers 99% of the population regardless of socioeconomic status (66 million). The SNDS was created for hospital payment and government purposes, and regular audits are conducted to ensure reliability and completeness. The SNDS also facilitates epidemiological research, with a specific interest in aging by an extended follow-up. Formal methods have been developed to assess the strengths and limitations of databases, and population-level data have enhanced our understanding of the use and outcomes of mechanical ventilation,[9] particularly for elderly patients hospitalized in ICUs in France.[12–14] The SNDS links the nationwide health insurance information system "SNIIRAM" to the national hospital discharge database of diagnosis-related groups (DRG) "PMSI," and to the national death registry "CépiDC." It contains comprehensive medical and administrative data for all patients in the country. This linkage of large-scale French national registry populations contributes to guiding public

decisions. Each patient is assigned a unique identification number with pseudonymized information, allowing individuals to be followed over time by linking inpatient and outpatient data from each hospitalization in all public or private facilities in France. Procedures, including surgery or life-sustaining treatments, are time-stamped and coded using a national classification system called CCAM (see the **Supplementary Appendix**).

The study was submitted to and approved by the independent national data protection authority (**CNIL Registration: 920181**). All data were deidentified for research purposes, and French law waives the need for informed consent. An independent institutional review board approved the study protocol (**IRB Registration: #00011928**).

STUDY POPULATION

All patients aged 80 years or older with complete data, admitted to hospitals in France from January 2013 through December 2018 (to avoid any ambiguities related to Covid-19), were eligible. We then selected ICU stays where the Simplified Acute Physiology Score (SAPS) II is comprehensively collected. To select the non-operative condition, we excluded stays that involved a surgery or whose DRG was surgical (or severe burn injury), either during the ICU stay or within 30 days prior to the ICU admission. To avoid counting multiple hospital outcomes for a single patient, only the first hospital stay including a medical admission to an ICU during the study period was considered for each patient. Finally, we considered the invasive condition for patients who underwent invasive mechanical ventilation (CCAM codes GLLD004, GLLD008, GLLD015) or vasopressor support (CCAM codes EQLF001, EQLF003) (**Table S2 in the Supplementary Appendix**).

VARIABLES, EXPOSURE AND OUTCOMES

The exposure variable was defined as the first occurrence of one of the following invasive procedures during the ICU stay: vasopressor support or invasive mechanical ventilation. We focused on these two main modifiable factors of interest because clinicians often question their benefit for the oldest

patients. This choice was also driven by their coding reliability, as there is a clear-cut bedside decision without delay, marking a turning point in the patient's trajectory. We did not include non-invasive ventilation because its use as a palliative treatment for dyspnea has become increasingly common. We also did not include renal replacement therapy due to the large grey area in coding between acute and chronic situations, and because its initiation can often be delayed without threatening the prognosis.[15] We addressed potential confounding resulting from variation in the case mix by controlling for age, severity of illness, pre-existing medical conditions expressed by the Charlson comorbidity index, primary diagnosis at admission, preadmission location, and academic status of the ICU. These confounders were specified a priori to develop a risk adjustment model for mortality. Patients were followed until death or the end of the year 2019, whichever occurred sooner. The invasive and non-invasive cohorts were mutually exclusive. One-year survival rate was the main outcome of interest. We also analyzed intermediate mortality rates and lengths of stays.

STATISTICAL ANALYSIS

Survival was measured from the date of ICU admission to the date of death or censored at the last follow-up. To limit immortal time bias, the occurrence of any invasive procedure was considered as a time-dependent covariate. Time precision was day, and the time of death was shifted by 0.1 day to avoid ties with the time of the procedure. Multivariate analysis of survival was performed by a Cox proportional hazards (PH) model producing hazard ratios (HR). The handling of ties used the Efron approximation. The PH assumption was verified by scaled Schoenfeld residuals. The time-varying effect of a procedure was modeled by adding an interaction term between the corresponding covariate and some transformation of time. The restricted mean survival time (RMST) method was selected because it is not dependent on the number of events and on the assumption of proportional hazards, as is the case in time-to-event analyses. RMST reflects the life expectancy of patients up to a specified time. Details regarding the statistical methods are provided in the **Supplementary Appendix**. As patients receiving invasive procedures may differ from the conservative ones, a

propensity score (PS) was used to minimize the effects of confounding. However, the population at risk changes over time due to attrition (death or discharge). Therefore, we used an inverse probability of treatment weighting (IPTW) method adapted to the time-dependent context.[16] IPTW usually estimates the average effect of treatment when the entire sample is moved from control to treated (ATE). But this seemed unrealistic for invasive support in the elderly population, so here IPTW targeted the average treatment effect in the treated (ATT). We divided the time span into strata within which a distinct PS could be calculated. These strata were each day until day 14, then periods 14-20, 20-30, every 15 days until 120, and then every 30 days until 365 (case base). This time-stratified PS was built using a Cox model that predicted the use of invasive procedures by variables available at admission. The influence of continuous variables (age and SAPS II) was modeled by fractional polynomials (FP). Variable balance was assessed by examining the standardized mean differences before and after weighting. Weights were trimmed at the first and 99th percentiles. To remove residual confounding, we combined weighting at the design stage with regression adjustment at the analysis stage when estimating treatment effects.[17] A robust sandwich-type estimator was used to calculate standard errors.

We performed sensitivity analyses to assess the robustness of the overall HR associated with invasive procedures: initially by using ATT weights truncated at the 5th and the 95th percentiles, then by using time strata defined by every day an invasive procedure or death occurred.

All tests were two-sided, and a p-value < 0.05 was considered statistically significant. The analysis used the SAS Enterprise Guide v7.15 (SAS Institute Inc., Cary, NC, USA) provided by the SNDS infrastructure.

RESULTS

The final analysis included 107 014 patients aged 80 years or older who were admitted to an ICU for medical reasons at 822 hospitals, mostly publicly funded (65%), in France between 2013 and 2018. Among those patients, 51 680 (48%) received invasive ventilation or vasopressors, and 55 334 (52%) received neither of the two. A flowchart of patients in the study is shown in **Figure 1**.

The demographic characteristics and the outcomes since ICU admission are shown in **Table 1**. The mean age was 84.6 years. More than half (52%) were male in the invasive group, and 52% were female in the conservative group. Overall, 89% were admitted from home, with most of them having a stop at the emergency department (59%). Patients in the invasive group had a significantly higher severity of illness at admission as reflected by a higher SAPS II but fewer general coexisting conditions as reflected by a lower Charlson comorbidity index. Over the years, the flow of patients was increasingly directed towards the invasive group. Among 51 680 (48%) patients in the invasive group, 70% were dead at one year, while among 55 334 (52%) patients in the conservative group, 41% were dead at one year ($p < 0.001$).

Outcomes of patients in the invasive group since ICU admission are detailed in **Table 2**. Among 38 427 patients who underwent vasopressors, 72% were dead at one year. Among 40 495 patients who received invasive ventilation, 72% were dead at one year. Patients who received a first invasive procedure were likely to receive the other one in 53% of cases, and one-year mortality was then 77%, whereas it was 60% and 63%, respectively, for vasopressors only or ventilation only. Among 8,761 patients who underwent renal replacement therapy (regardless of the group), 74% were dead at one year. The median number of days in the ICU was 4 (interquartile range 2 – 8). The median number of days in the hospital was 8 (interquartile range 2 – 16). The median duration of ventilation was 3 days (interquartile range 2 – 7). There were 2582 patients who underwent prone-positioning. In their case, the median number of sessions was 2 (interquartile range 1 – 3) per patient. The

median duration of vasopressor support was 2 days (interquartile range 1 – 4). The time of the initial invasive procedure was the day of ICU admission for 79% of patients in the invasive group and the following day for an additional 9% (**Figure S1 in the Supplementary Appendix**). More than half of the patients in the invasive group had both procedures, generally on the same day (86%). If vasopressors predated ventilation (6%) or ventilation predated vasopressors (9%), the median interval of initiation was 1 day (interquartile range 1 – 3). 24% of deaths in the invasive group occurred on the day of the initiation of any procedure, and 7% the following day.

After the calculation of the time-stratified PS, the balance obtained on ATT weighted samples was good, with absolute standardized differences less than 0.1 (**Figure S2 in the Supplementary Appendix**). The test of Schoenfeld residuals for the proportional hazards assumption was significant, as the HR was decreasing along time (**Figure S4 in the Supplementary Appendix**). Kaplan-Meier survival curves obtained before and after the time-stratified ATT weighting are presented in **Figure 2**. ATT weighting induced a decrease in one-year survival rate in the conservative group from 59% to 43% (95% CI, 0.421 to 0.441) vs. 27% in the invasive group (95% CI, 0.268 to 0.276, remained unchanged after ATT weighting, as expected). The mortality in the invasive group remained significantly higher after time-dependent IPTW (HR, 1.64; 95% CI, 1.60 to 1.69, $p < 0.001$). Life expectancy limited to one year was 117.5 days in the invasive group versus 185.2 days in the conservative group, resulting in a significant loss of 67.7 days (RMST, 95% CI, 65.7 to 69.8).

In the sensitivity analysis, neither the use of ATT weights truncated at the 5th and 95th percentiles nor the use of a different time-stratification pattern changed substantially the HR associated with invasive procedures. Finally, the combination of weighting and further adjustment on baseline covariates (year, age, sex, coexisting conditions, admission source, severity, and academic status) produced a similar hazard ratio (HR, 1.67; 95% CI, 1.63 to 1.73, $p < 0.001$). (**See the Supplementary Appendix**).

DISCUSSION

Several studies support conservative management over invasive approaches,[15,18,19] and there is concern that invasive procedures may worsen the prognosis of older ICU patients.[20,21] Our large nationwide study was designed to describe the association between invasive care and mortality in real-world clinical practice. Our findings suggest that invasive procedures are a negative determinant, but as an observational study, it cannot be concluded as evidence of harm or non-inferiority between the two groups.

However, the high mortality rate in the invasive group is *per se* our main finding. With a one-year survival rate of 27%, it seems reasonable that a large portion of elderly patients may not be best served by invasive care. This calls into question the upward trend of time-limited trials that could lead to ethical misunderstanding, especially as the survival curves separated early on with a rapid decrease in the invasive group.

The strength of this study is the size of the cohort with few missing data and the national-level database needed to overcome sampling biases[22] that often limit epidemiological studies of the critically ill elderly. With 107,014 patients under observation, we had the statistical power to robustly assess this issue in the target population of medical ICU patients adjusted for known prognostic factors specified a priori. The comprehensive multicenter design enhances the generalizability of our findings, particularly important given that older patients are frequently excluded from clinical trials[23] but are commonly treated in the ICU. Our study further provides valuable information on the epidemiology of circulatory and respiratory failures in older patients.

Limitations of our study include potential biases due to coding errors or unmeasured confounders. Moreover, our study did not include the functional status nor quality of life among survivors, which

are more important than survival for many older persons.[24–26] The study also lacks consideration for preexisting frailty, despite its recognized importance as a determinant of mortality.[27–29] However, while elderly patients with a higher functional baseline are more likely to survive, their chances of returning to their prior level are reduced compared to those with a lower functional baseline.[30,31] In addition, whoever with a good functional status is resuscitated until it becomes poor is doomed to die with a poor functional status.

The absence of consideration for triage process, treatment appropriateness, or therapeutic limitations may introduce selection bias but reflects the real-world shared decision-making process among physicians, patients, and families. Current studies suggest that the risk of overutilization of invasive procedures outweighs the risk of underutilization[19,21,32–34]

The "*Principles of Biomedical Ethics*" by Beauchamp and Childress, developed in 1979 the four principles of medical care: autonomy, non-maleficence, beneficence, and justice. Individuals have a significant preference for non-maleficence over the other principles, but it does not appear to be directly utilized in the decision-making process.[35] Advance care planning is essential to support clinicians in targeting appropriate invasive, rehabilitative, or palliative strategies which are not exclusive. As stated in a recent review: all critically ill patients, by definition, have serious illness and thus have palliative care needs.[36] The retrospective meaning of "end-of-life care" seems problematic unless considering the oldest patients are living the last part of their lives. Oldest patients, similar to pediatric patients, have distinct healthcare trajectories and goals supported by physiological evidence for geriatric specificities.

To clarify, our study does not suggest that elderly patients should be denied ICU admission. On the contrary, it highlights the potential benefits of an intensive integrative approach in the ICU rather than a purely technical approach that may only prolong the dying process.[37] The conservative group exhibits a low mortality rate, including patients who were refused invasive treatments due to futility,

and it is unlikely to be further reduced with a more invasive approach. Similarly, the high mortality rate observed in the invasive group is unlikely to be exacerbated by a less aggressive strategy.

Our findings have strong ethical implications. Despite being highly selected for favorable outcomes in real-world practice, patients who received invasive procedures had a low survival rate. The incentive care policy for a standard of care regardless of age is questionable in the light of medical appropriateness[19,21,32–34] and patients' wishes.[24–26] While age should not be the sole criterion for ICU triage, the combination of age and the need for an invasive procedure must be considered attentively when deciding on treatment options. Growing evidence suggests a gap between patient preferences and the actual care provided.[38] Age remains a potent trigger for clinicians to ensure that patients and families are well-informed about the benefits, risks, and harms associated with invasive care.[39]

CONCLUSIONS

In conclusion, in our nationwide study, an invasive approach was associated with a lower one-year survival rate among elderly patients who were admitted to the ICU for medical reasons compared to a conservative approach. Early discussion, including the requirement for an invasive procedure, may reduce the incidence of avoidable aggressive end-of-life care and improve goal-concordant care achievement.

AUTHOR CONTRIBUTIONS

This analysis is an investigator-initiated study led by Clement Leclaire, he supervised the analyses, drafted the manuscript and is the guarantor. All co-authors contributed to the study design and made substantial contribution. AG and CL conceptualised the study and prepared the original study protocol, which was subsequently reviewed by MDS and PA. CL, AG and PA developed the statistical methods. CL and PA had full access to the data, and take responsibility for the integrity of the data and accuracy of the analysis. All authors contributed to data interpretation, critically revised the drafted manuscript and approved the final submitted version. The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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CONFLICT OF INTEREST DISCLOSURES

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

ETHICS APPROVAL/ TRANSPARENCY / PATIENT AND PUBLIC INVOLVEMENT STATEMENT

The study was submitted to and approved by the independent national data protection authority (**CNIL Registration: 920181**). All data were deidentified for research purposes, and French law waives the need for informed consent. An independent institutional review board approved the study protocol (**IRB Registration: #00011928**). The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned have been explained. Patients and the public were not involved in the research we are describing.

FUNDING/SUPPORT AND ROLE

This study was supported by Assistance Publique–Hôpitaux de Paris through an agreement between the CNAM (Caisse Nationale d'Assurance Maladie) and HAD-APHP (signed on October 19, 2020) for the OCTO-Reverse project (962976). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

DATA SHARING

The SNDS (Système National des Données de Santé) data used in this paper are held by the CNAM. Access to the data can be requested under data access conditions through SNDS/DEMEX/n° TPS 962976.

REFERENCES

1. Vallet H, Schwarz GL, Flaatten H, de Lange DW, Guidet B, Dechartres A. Mortality of Older Patients Admitted to an ICU: A Systematic Review. Crit Care Med. 2021;49(2):324-334. doi:10.1097/CCM.0000000000004772

2. Boumendil A, Latouche A, Guidet B, ICE-CUB Study Group. On the benefit of intensive care for very old patients. Arch Intern Med. 2011;171(12):1116-1117. doi:10.1001/archinternmed.2011.102

3. Biddison LD, Berkowitz KA, Courtney B, et al. Ethical Considerations: Care of the Critically Ill and Injured During Pandemics and Disasters: CHEST Consensus Statement. Chest. 2014;146(4, Supplement):e145S-e155S. doi:10.1378/chest.14-0742

4. Guidet B, Vallet H, Boddaert J, et al. Caring for the critically ill patients over 80: a narrative review. Ann Intensive Care. 2018;8(1):114. doi:10.1186/s13613-018-0458-7

5. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. JAMA Intern Med. 2015;175(4):523-529. doi:10.1001/jamainternmed.2014.7889

6. Flaatten H, de Lange DW, Artigas A, et al. The status of intensive care medicine research and a future agenda for very old patients in the ICU. Intensive Care Med. 2017;43(9):1319-1328. doi:10.1007/s00134-017-4718-z

7. Seethala RR, Blackney K, Hou P, et al. The Association of Age With Short-Term and Long-Term Mortality in Adults Admitted to the Intensive Care Unit. J Intensive Care Med. 2017;32(9):554-558. doi:10.1177/0885066616658230

8. Nathanson BH, Higgins TL, Brennan MJ, Kramer AA, Stark M, Teres D. Do elderly patients fare well in the ICU? Chest. 2011;139(4):825-831. doi:10.1378/chest.10-1233

9. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA. 2010;303(9):849-856. doi:10.1001/jama.2010.216

10. Jubran A, Grant BJB, Duffner LA, et al. Long-Term Outcome after Prolonged Mechanical Ventilation. A Long-Term Acute-Care Hospital Study. Am J Respir Crit Care Med. 2019;199(12):1508-1516. doi:10.1164/rccm.201806-1131OC

11. Biston P, Aldecoa C, Devriendt J, et al. Outcome of elderly patients with circulatory failure. Intensive Care Med. 2014;40(1):50-56. doi:10.1007/s00134-013-3121-7

12. Fassier T, Duclos A, Abbas-Chorfa F, et al. Elderly patients hospitalized in the ICU in France: a population-based study using secondary data from the national hospital discharge database. J Eval Clin Pract. 2016;22(3):378-386. doi:10.1111/jep.12497

13. Atramont A, Lindecker-Cournil V, Rudant J, et al. Association of Age With Short-term and Long-term Mortality Among Patients Discharged From Intensive Care Units in France. JAMA Netw Open. 2019;2(5):e193215. doi:10.1001/jamanetworkopen.2019.3215

14. Laporte L, Hermetet C, Jouan Y, et al. Ten-year trends in intensive care admissions for respiratory infections in the elderly. Ann Intensive Care. 2018;8(1):84. doi:10.1186/s13613-018-0430-6

15. Gaudry S, Hajage D, Schortgen F, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;375(2):122-133. doi:10.1056/NEJMoa1603017

16. Hernán MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. Stat Med. 2002;21(12):1689-1709. doi:10.1002/sim.1144

17. Austin PC, Thomas N, Rubin DB. Covariate-adjusted survival analyses in propensity-score matched samples: Imputing potential time-to-event outcomes. Stat Methods Med Res. 2020;29(3):728-751. doi:10.1177/0962280218817926

18. Auriemma CL, Van den Berghe G, Halpern SD. Less is more in critical care is supported by evidence-based medicine. Intensive Care Med. 2019;45(12):1806-1809. doi:10.1007/s00134-019-05771-2

19. Chang DW, Shapiro MF. Association Between Intensive Care Unit Utilization During Hospitalization and Costs, Use of Invasive Procedures, and Mortality. JAMA Intern Med. 2016;176(10):1492-1499. doi:10.1001/jamainternmed.2016.4298

20. Guidet B, Leblanc G, Simon T, et al. Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France: A Randomized Clinical Trial. JAMA. 2017;318(15):1450-1459. doi:10.1001/jama.2017.13889

21. Sjoding MW, Prescott HC, Wunsch H, Iwashyna TJ, Cooke CR. Hospitals with the highest intensive care utilization provide lower quality pneumonia care to the elderly. Crit Care Med. 2015;43(6):1178-1186. doi:10.1097/CCM.0000000000000925

22. Hua M, Gershengorn HB, Wunsch H. Assessing delivery of mechanical ventilation: risks and benefits of large databases. Intensive Care Med. Published online August 26, 2020:1-4. doi:10.1007/s00134-020-06214-z

23. Ivie RMJ, Vail EA, Wunsch H, Goldklang MP, Fowler R, Moitra VK. Patient Eligibility for Randomized Controlled Trials in Critical Care Medicine: An International Two-Center Observational Study*. Critical Care Medicine. 2017;45(2):216. doi:10.1097/CCM.0000000000002061

24. Philippart F, Vesin A, Bruel C, et al. The ETHICA study (part I): elderly's thoughts about intensive care unit admission for life-sustaining treatments. Intensive Care Med. 2013;39(9):1565-1573. doi:10.1007/s00134-013-2976-y

25. Behforouz HL, Drain PK, Rhatigan JJ. Rethinking the Social History. New England Journal of Medicine. 2014;371(14):1277-1279. doi:10.1056/NEJMp1404846

26. Le Guen J, Boumendil A, Guidet B, Corvol A, Saint-Jean O, Somme D. Are elderly patients' opinions sought before admission to an intensive care unit? Results of the ICE-CUB study. Age Ageing. 2016;45(2):303-309. doi:10.1093/ageing/afv191

27. Flaatten H, De Lange DW, Morandi A, et al. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). Intensive Care Med. 2017;43(12):1820-1828. doi:10.1007/s00134-017-4940-8

28. Guidet B, de Lange DW, Boumendil A, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. Intensive Care Med. Published online November 29, 2019. doi:10.1007/s00134-019-05853-1

29. Muscedere J, Waters B, Varambally A, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med. 2017;43(8):1105-1122. doi:10.1007/s00134-017-4867-0

30. Heyland DK, Garland A, Bagshaw SM, et al. Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. Intensive Care Med. 2015;41(11):1911-1920. doi:10.1007/s00134-015-4028-2

31. Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care. 2013;17(3):R100. doi:10.1186/cc12745

32. Teno JM, Gozalo P, Khandelwal N, et al. Association of Increasing Use of Mechanical Ventilation Among Nursing Home Residents With Advanced Dementia and Intensive Care Unit Beds. JAMA Intern Med. 2016;176(12):1809-1816. doi:10.1001/jamainternmed.2016.5964

33. Sullivan DR, Kim H, Gozalo PL, Bunker J, Teno JM. Trends in Noninvasive and Invasive Mechanical Ventilation Among Medicare Beneficiaries at the End of Life. JAMA Intern Med. Published online October 19, 2020. doi:10.1001/jamainternmed.2020.5640

34. Guidet B, Flaatten H, Boumendil A, et al. Withholding or withdrawing of life-sustaining therapy in older adults (≥ 80 years) admitted to the intensive care unit. Intensive Care Med. 2018;44(7):1027-1038. doi:10.1007/s00134-018-5196-7

35. Page K. The four principles: Can they be measured and do they predict ethical decision making? BMC Med Ethics. 2012;13:10. doi:10.1186/1472-6939-13-10

36. Aslakson RA, Cox CE, Baggs JG, Curtis JR. Palliative and End-of-Life Care: Prioritizing Compassion Within the ICU and Beyond. Critical Care Medicine. 2021;49(10):1626-1637. doi:10.1097/CCM.0000000000005208

37. Cox CE, Curtis JR. Using Technology to Create a More Humanistic Approach to Integrating Palliative Care into the Intensive Care Unit. Am J Respir Crit Care Med. 2016;193(3):242-250. doi:10.1164/rccm.201508-1628CP

38. Heyland DK, Dodek P, Mehta S, et al. Admission of the very elderly to the intensive care unit: family members' perspectives on clinical decision-making from a multicenter cohort study. Palliat Med. 2015;29(4):324-335. doi:10.1177/0269216314566060

39. Leblanc G, Boumendil A, Guidet B. Ten things to know about critically ill elderly patients. Intensive Care Med. 2017;43(2):217-219. doi:10.1007/s00134-016-4477-2

TABLE 1. Characteristics of the Patients*

	All Patients (N = 107 014)	Invasive Group (N = 51 680)	Conservative Group (N = 55 334)	P Value
Percentage of patients	100	48	52	
Mean age – Yr	84.6 ± 3.6	84.3 ± 3.4	84.9 ± 3.7	< 0.001
Male sex – no (%)	53 457 (50)	26 785 (52)	26 672 (48)	< 0.001
Year of enrollment – no (%)				< 0.001
2013	17 138 (16)	7 756 (15)	9 382 (17)	
2014	17 484 (16)	8 013 (16)	9 471 (17)	
2015	18 286 (17)	8 612 (17)	9 674 (18)	
2016	18 312 (17)	9 143 (18)	9 169 (17)	
2017	18 284 (17)	9 236 (18)	9 048 (16)	
2018	17 510 (16)	8 920 (17)	8 590 (16)	
Admission source – no (%)				< 0.001
Home	31 703 (30)	15 079 (29)	16 624 (30)	
Emergency department	63 032 (59)	30 446 (59)	32 586 (59)	
Other skilled facility	12 279 (11)	6 155 (12)	6 124 (11)	
Hospital status – no (%)				< 0.001
Private	17 411 (16)	5 226 (10)	12 185 (22)	
Public academic	28 394 (27)	15 024 (29)	13 370 (24)	
Public non-academic	61 209 (57)	31 430 (61)	29 779 (54)	
Geriatric team in the hospital – no (%)	78 973 (74)	41 717 (81)	37 256 (67)	< 0.001
Palliative care team in the hospital – no (%)	61 089 (57)	33 089 (64)	28 000 (51)	< 0.001
Coexisting conditions – no (%)				< 0.001
Cardiac Disease	39 659 (37)	18 384 (36)	21 275 (39)	
Respiratory disease	31 807 (30)	14 046 (27)	17 761 (32)	
Renal disease	28 344 (27)	12 937 (25)	15 407 (28)	
Neurologic disease	12 062 (11)	6 305 (12)	5 757 (10)	

Cognitive impairment	10 651 (10)	4 996 (10)	5 655 (10)	
Cirrhosis	3 622 (3)	1 936 (4)	1 686 (3)	
Diabetes	16 191 (15)	7 723 (15)	8 468 (15)	
Cancer	19 162 (18)	9 083 (18)	10 079 (18)	
Charlson comorbidity index (CCI)				< 0.001
Median (Interquartile range)	2 (1 – 4)	2 (1 – 4)	2 (1 – 4)	
CCI = 0	23 972 (22%)	12 698 (25%)	11 274 (20%)	
Immunodeficiency – no (%)	20 753 (19)	9 884 (19)	10 869 (20)	< 0.001
Median SAPS II – (Interquartile range)	45 (34 – 63)	59 (45 – 76)	37 (30 – 46)	< 0.001
Diagnosis category – no (%)				< 0.001
Circulatory	40 189 (38)	20 773 (40)	19 416 (35)	
Respiratory	29 926 (28)	13 682 (27)	16 244 (29)	
Neuro-metabolic	36 899 (35)	17 225 (33)	19 674 (36)	
Outcomes†				< 0.001
One-year mortality – no (%)	58 955 (55)	36 019 (70)	22 936 (41)	
ICU mortality – no (%)	32 160 (30)	26 152 (51)	6 008 (11)	
In-hospital mortality – no (%)	37 354 (35)	28 438 (55)	8 916 (16)	
Median length of stay – days (interquartile range)				< 0.001
In ICU	4 (2 – 8)	5 (2 – 11)	3 (1 – 6)	
In hospital	8 (2 – 16)	7 (1 – 18)	8 (3 – 14)	
ICU readmission within the year – no (%)				< 0.001
In patients from enrollment	23 846 (22)	6 894 (13)	16 952 (31)	
In ICU-survivors	23 846 (32)	6 894 (27)	16 952 (34)	
Hospital discharge for survivors – no (%)				< 0.001
Home	35 312 (51)	9 016 (39)	26 296 (57)	
Other skilled facility	34 348 (49)	14 226 (61)	20 122 (43)	

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.

† Crude unweighted outcomes since ICU admission, without regard for the time-to-event analysis.

TABLE 2. Outcomes in the Invasive Group (n = 51 680)*

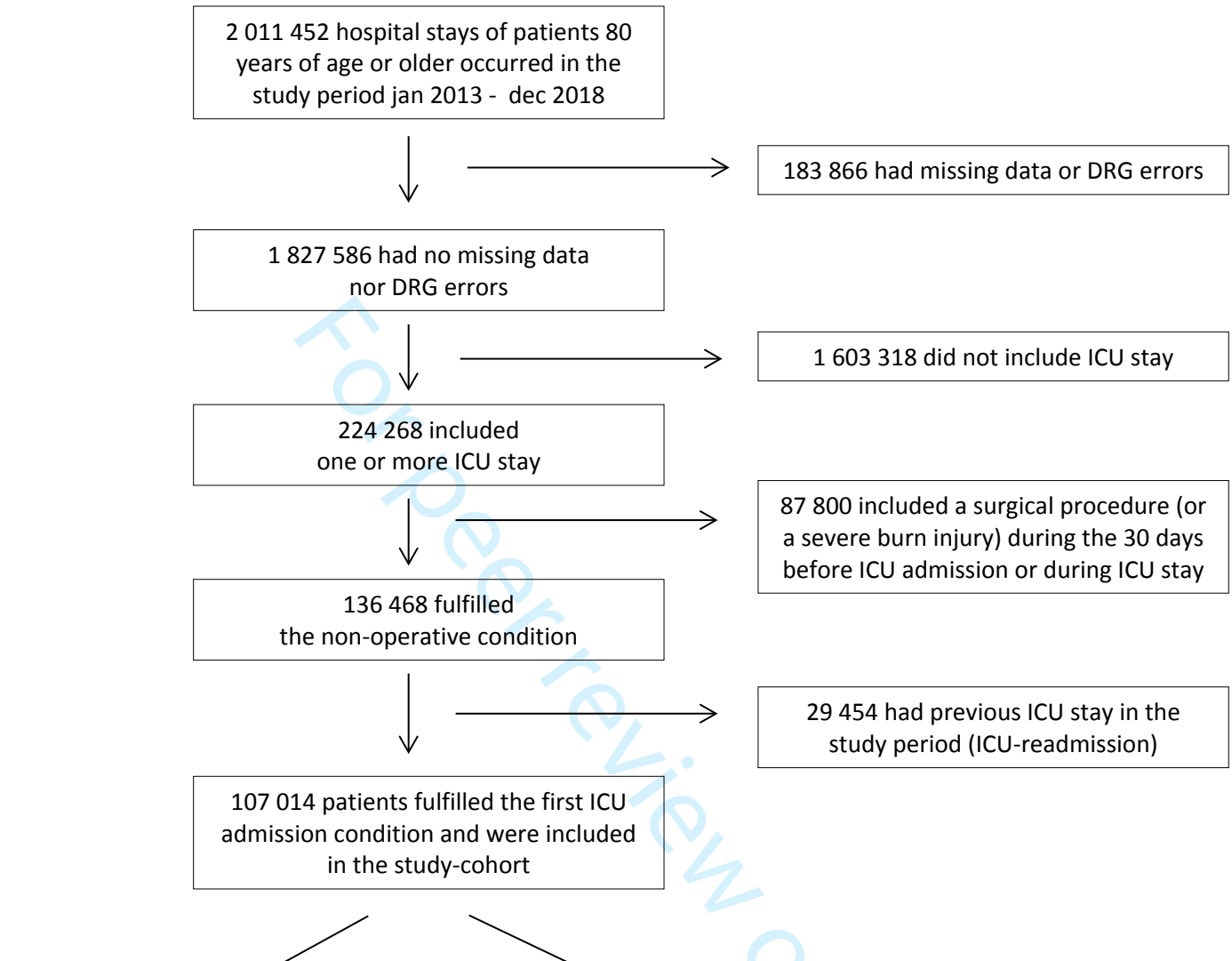
	No (%)	Mortality – no (%)			Median length of stay – days (interquartile range)	
		ICU	**Hospital**	**1 Year**	**ICU**	**Hospital**
All vasopressors (± ventilations)	38 427 (74)	20 606 (54)	22 281 (58)	27 694 (72)	5 (2 – 12)	8 (3 – 18)
All ventilations (± vasopressors)	40 495 (78)	22 632 (56)	24 217 (60)	29 331 (72)	5 (2 – 12)	7 (1 – 18)
Vasopressors only	11 185 (22)	3 520 (32)	4 221 (38)	6 688 (60)	5 (2 – 8)	9 (2 – 17)
Ventilations only	13 253 (26)	5 546 (42)	6 157 (47)	8 325 (63)	4 (2 – 9)	9 (3 – 18)
Vasopressors and ventilations	27 242 (53)	17 086 (63)	18 060 (66)	21 006 (77)	6 (2 – 14)	7 (2 – 16)

* Crude incidence and unweighted outcomes since ICU admission, without regard for the time-to-event analysis.

Percentages may not sum to 100 because of rounding.

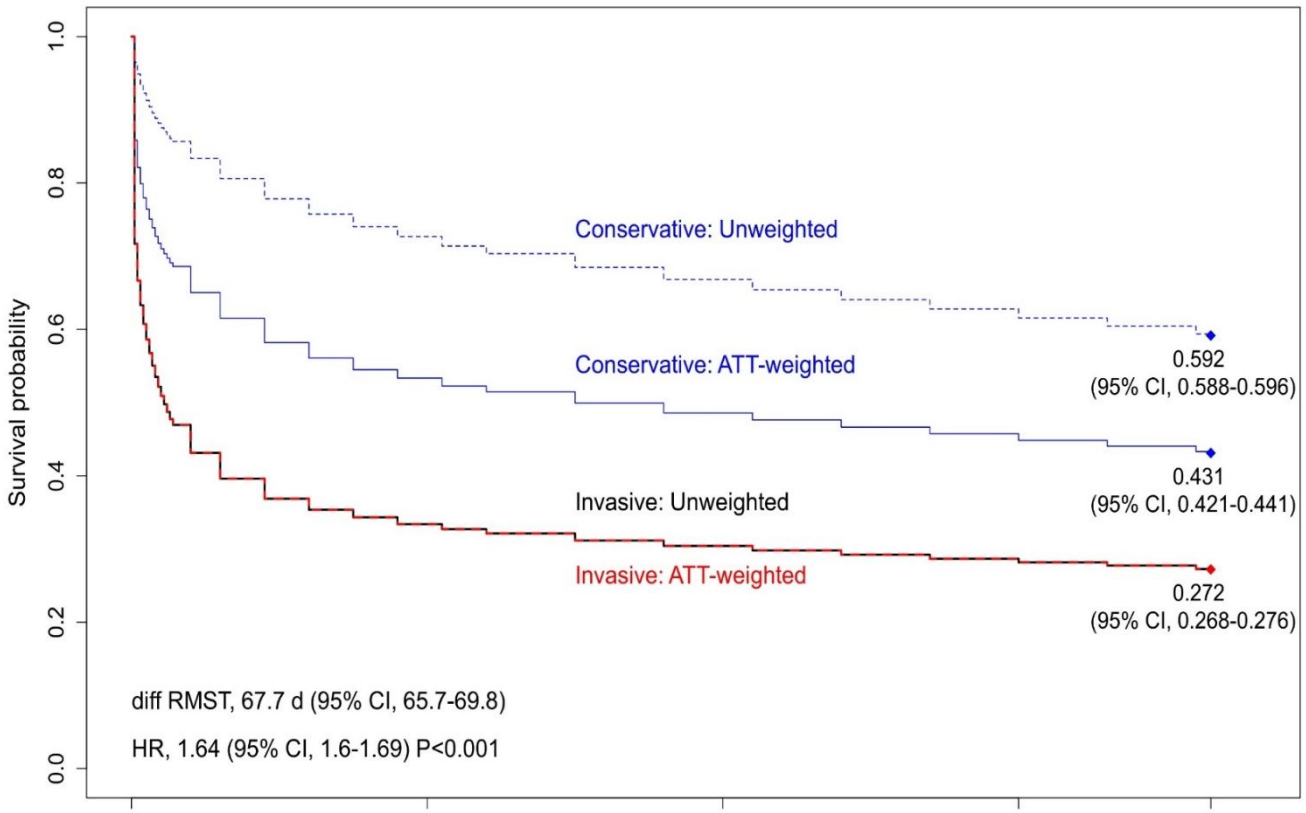
Footnote: This table reports the subsets of patients according to the invasive procedures exposure.

FIGURE 1. Flowchart of Patients in the Study



Footnote: ICU denotes intensive care unit, and DRG diagnosis-related-groups

FIGURE 2. Probability of Survival from ICU admission to One Year, according to Conservative or Invasive Approach, Before and After Time-Dependent Propensity Score Weighting (ATT).



Footnote: Kaplan-Meier method adapted to time-dependant covariate (with 95% CI). Dashed lines represent time-dependent Kaplan-Meier plot of the probability of survival from ICU admission to one year among the original unweighted population. Solid lines represent time-dependent Kaplan-Meier plot of the probability of survival on IPTW-ATT weighted sample using weights trimmed at the first and 99th percentile. Invasive curve remained unchanged after weighting, as expected. IPTW denotes inverse probability of treatment weighting, ATT denotes average treatment effect in the treated, HR denotes the hazard ratio obtained from the ATT99 weighted Cox model and diff-RMST the difference in (one-year) restricted mean survival time (days).

SUPPLEMENTARY APPENDIX

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LIST OF INVESTIGATORS AND CONTRIBUTION

This analysis is an investigator-initiated study led by Clement Leclaire, he supervised the analyses, drafted the manuscript and is the guarantor. All co-authors contributed to the study design and made substantial contribution. AG and CL conceptualised the study and prepared the original study protocol, which was subsequently reviewed by MDS and PA. CL, AG and PA developed the statistical methods. CL and PA had full access to the data, and take responsibility for the integrity of the data and accuracy of the analysis. All authors contributed to data interpretation, critically revised the drafted manuscript and approved the final submitted version.

METHODOLOGICAL PLAN

Detailed description of data source - the SNDS Database

We conducted a nationwide retrospective analysis of data prospectively collected in the Système National des Données de Santé (SNDS), the national French health care database that covers around 99% of the population. The SNDS was created to answer epidemiological research questions with specific interests in occupational and social factors, chronic diseases, and aging, including a medico-economic assessment and extended follow-up without attrition bias **[1,2]**.

Using the National hospital discharge database is an established method for elderly patients hospitalized in the ICU in France **[3–5]**. Formal methods have been developed to assess the strengths and limitations of databases **[6,7]**, and population-level data have greatly enhanced our understanding of how mechanical ventilation is utilized and the associated outcomes for patients **[8]**.

The SNDS links the Système National d'Information Interrégimes de l'Assurance Maladie (SNIIRAM), the nationwide health insurance information system, to the national hospital discharge database of Diagnosis-Related Groups (DRG) **[9,10]**, known as Programme de Médicalisation des Systèmes d'Information (PMSI), and to the national death registry, "CépiDC." It includes more than 99% of the French population (66 million people) from birth (or immigration) to death (or emigration), regardless of changes in occupation, retirement, or socioeconomic status. Therefore, the SNDS contains individual pseudonymized information on all medical and paramedical encounters, drug claims, hospital admissions and procedures, as well as the date and cause of death, which are linked to create an individual longitudinal record. This linkage of large-scale national registry populations in France contributes to guiding public decisions **[11,12]**.

The SNDS collects comprehensive medical and administrative data prospectively for all patients in the country and underlies the activity-based hospital payment system. All patients are assigned a unique identification number, allowing for longitudinal follow-up by linking inpatient and outpatient data from each hospitalization in all public or private facilities in France. Hospital data include age, sex, admission and discharge dates and location, vital status at discharge, hospital units visited during the hospitalization, and length of hospitalization. Hospital discharge diagnoses (main, associated, secondary) provide information on the reason for admission (main) and background risk modifiers (e.g., diabetes, renal failure, coronary heart disease) that complicate the care. Associated diagnoses provide information on the reasons for procedures as the main diagnosis. Procedures, both surgical and medical, including life-sustaining treatments, are time-stamped and coded using a national multidimensional classification system called CCAM **[13]**.

These data are utilized for hospital payment **[14]** and government purposes **[12]**, so the quality of coding undergoes regular internal and external audits, both within the hospital information systems and through the national healthcare system's accreditation process **[15]**. Both reliability and completeness are excellent, and a structured assessment of the database has been described elsewhere **[3]**.

Detailed description of statistical analysis

Baseline characteristics of patients were described as frequencies and percentages for categorical variables and as means (with standard deviations, SD) or medians (with interquartile range, IQR) for continuous variables. Bivariate associations were evaluated using the Kruskal-Wallis test for continuous variables and the $\chi 2$ or Fisher exact test for categorical variables, as appropriate. Survival was measured from the date of ICU admission to the date of death or censored at the last follow-up. Since the refreshment of SNDS is periodic across the entire country, the date of the last follow-up was estimated by the 95th percentile of the dates of death.

To limit an immortal time bias, the occurrence of any invasive procedure was considered as a time-dependent covariate. Time precision was at the day level, and the time of death was shifted by 0.1 day to avoid ties with the time of the procedure. Multivariate analysis of survival was performed using a Cox proportional hazards (PH) model, which produced hazard ratios (HR). The handling of ties used the Efron approximation. The PH assumption was verified by scaled Schoenfeld residuals. The Cox model was extended to deal with time-varying effects by adding an interaction term between the given covariate and some transformation of time (step function, continuous power transformation such as first-degree fractional polynomials, or stratification of time). The touchstone for choosing the best approach was the Akaike Information Criterion (AIC) **[16]**. When the effect was time-varying, a unique overall HR was interpreted as a weighted average HR over the event times **[17]**. However, we also summarized this effect with a model-free parameter, the difference in the restricted mean survival time (RMST), which has greater clinical interpretability and represents the loss of life expectancy **[18,19]**.

As patients receiving invasive procedures may differ from conservative ones, a propensity score (PS) was used to minimize the effects of confounding. However, the population at risk changes due to attrition of susceptibles. The conventional method may cause bias with the time-varying exposure because those time-dependent treatment decisions act as time-varying confounders, affecting both the occurrence of the event of interest and the patient's exposure to the treatment of interest **[20]**. Thus, the conventional PS analysis must become time-dependent to address this time-varying effect and be able to estimate measures of effect similar to those obtained in randomized experiments **[21,22]**. To accommodate this, our study made use of the inverse probability of treatment weighting (IPTW) method adapted to the time-dependent context **[23]**.

IPTW usually estimates the average treatment effect (ATE) when the entire sample is moved from control to treated. However, this seemed unrealistic for invasive support in the elderly population. Therefore, IPTW targeted the average treatment effect in the treated (ATT) **[24]**, also called weighting by odds, which denotes the average effect of treatment in those subjects who were ultimately treated, as PS matching does. In such a case, the analysis uses the treated subjects as the reference population to which each group is standardized.

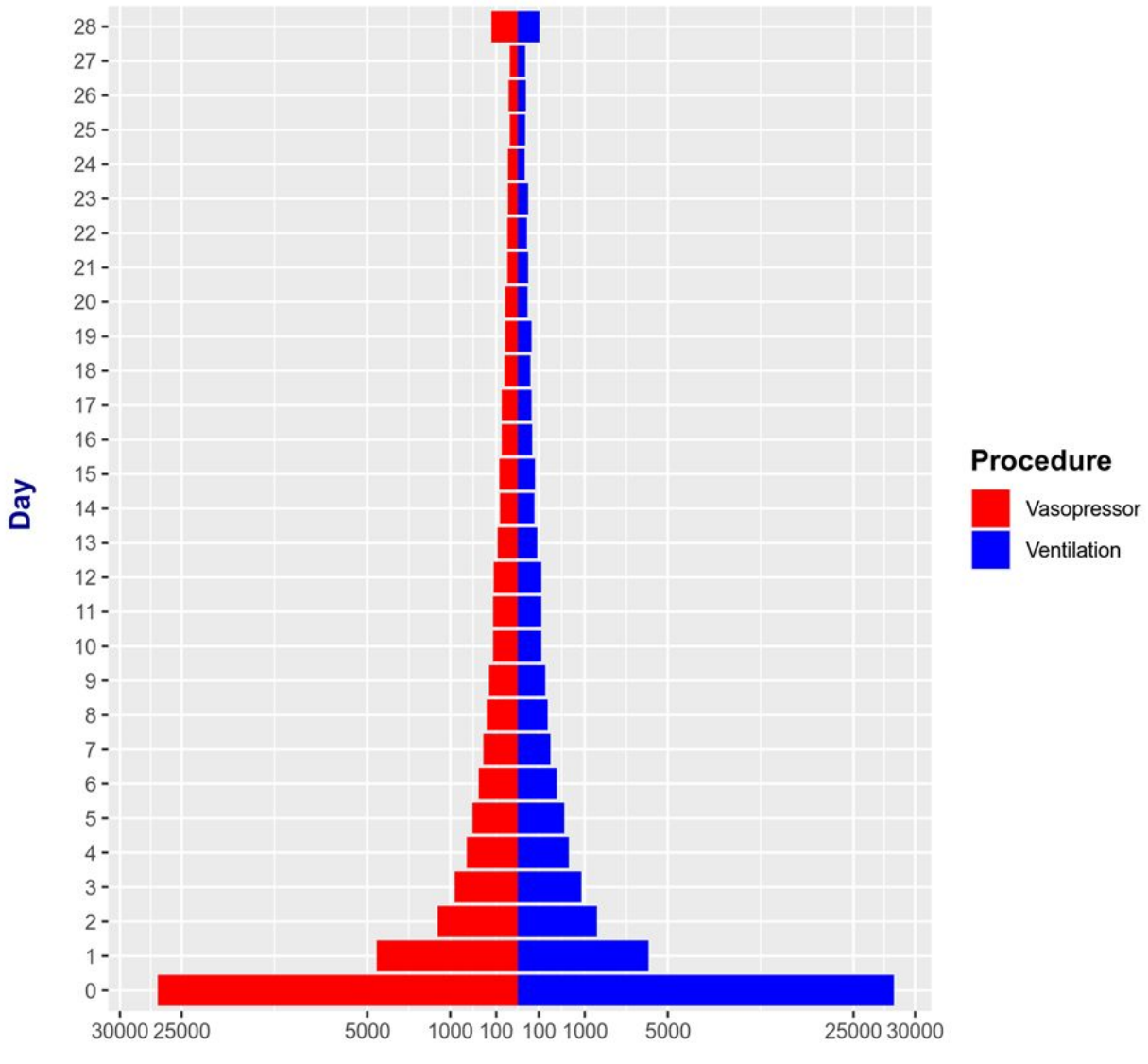
We divided the time span into strata within which a PS was calculated. These strata included each day until day 14, then periods of 14-20, 20-30, every 15 days until 120, and every 30 days until 365 (case base). This time-stratified PS was built using a Cox model that predicted the use of invasive procedures based on variables available at admission. The influence of continuous variables (age and SAPS-II) was modeled by fractional polynomials (FP). Variable balance was assessed by examining the standardized mean differences before and after weighting **[25]**. Weights were trimmed at the first and 99th percentiles. To remove residual confounding, we combined weighting at the sampling stage with regression adjustment at the analysis stage when estimating treatment effects **[26]**. A robust sandwich-type estimator was used to calculate standard errors.

We performed sensitivity analyses to assess the robustness of the overall HR associated with invasive procedures: initially by using ATT weights truncated at the 5th and 95th percentiles, and then by using time strata defined by every day an invasive procedure or death occurred.

All tests were two-sided, and a p-value < 0.05 was considered statistically significant. The analysis was conducted using SAS Enterprise Guide v7.15 (SAS Institute Inc., Cary, NC, USA) provided by the SNDS infrastructure.

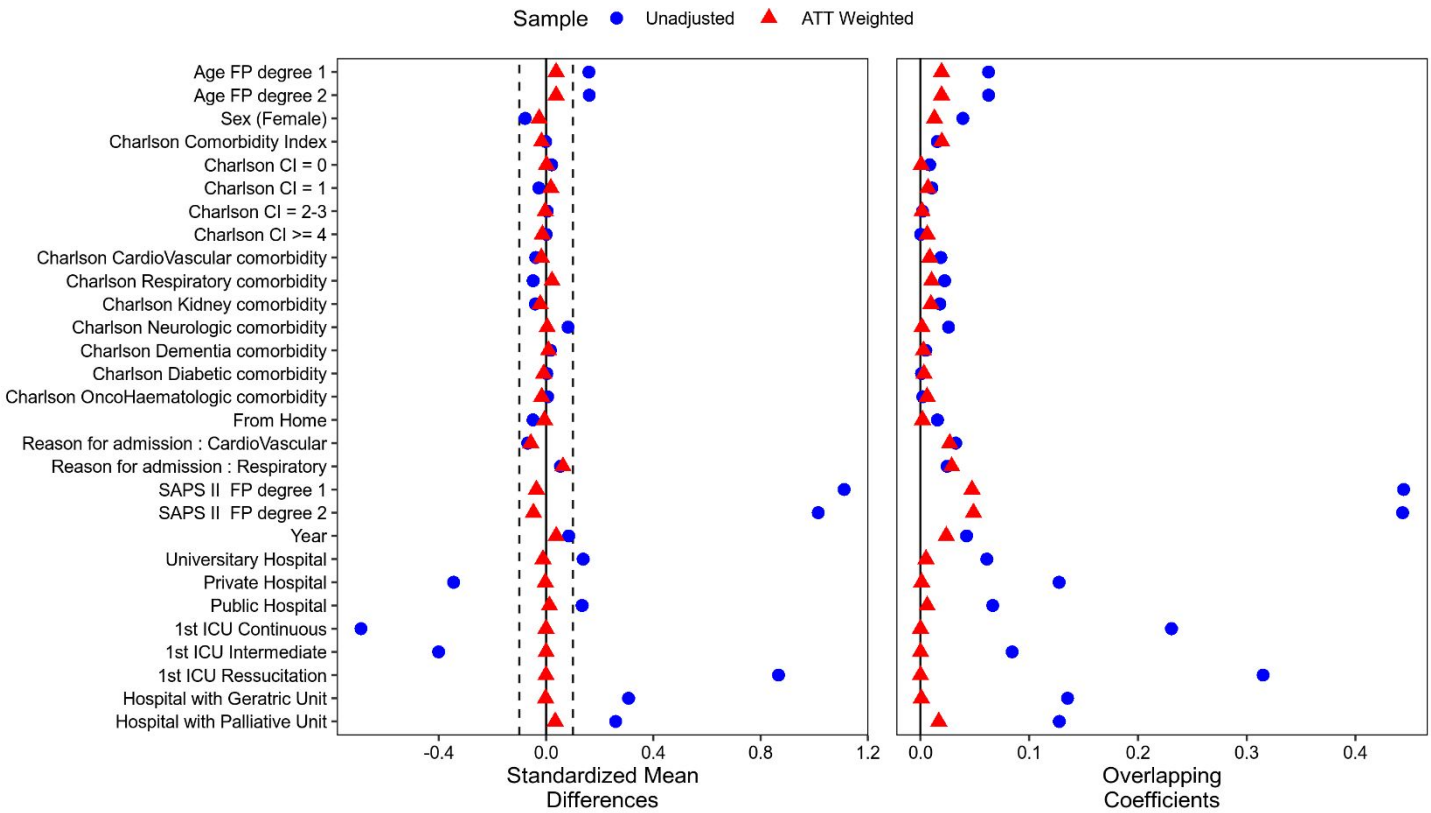
FIGURES

Figure S1: Time until initiation of the invasive procedure since ICU admission (In the invasive group)



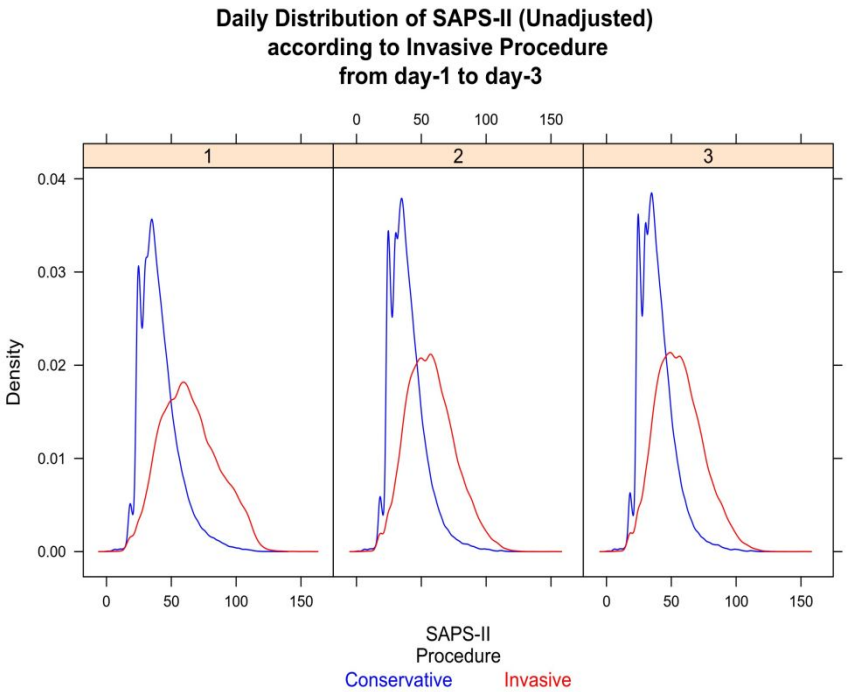
In the invasive group: Number of stays according to the day of initiation of the invasive procedure from ICU-admission (note that the bars at day-28 include stays beyond day-28): Time of initial vasopressor support was the day of ICU-admission for 75% of patients and the following day for 11% more. Time of initial ventilation support was the day of ICU-admission for 77% of patients and the following day for 9% more.

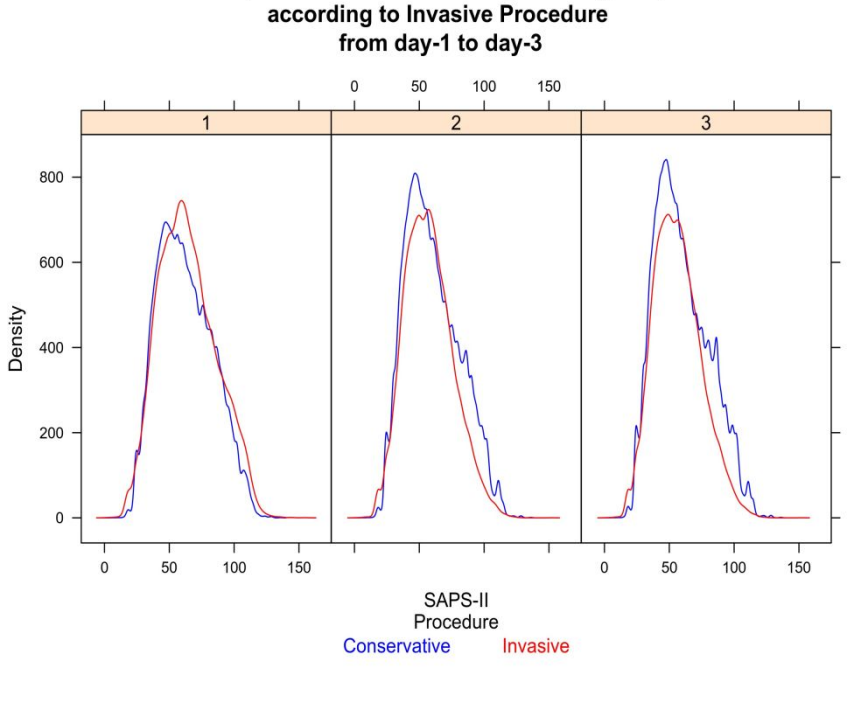
Figure S2: Covariate balance on the whole period



While there were significant differences between invasive and conservative patients in the raw sample, differences in the ATT weighted sample issued from the time-stratified model were minimal, with absolute standardized differences less than 0.1 as shown on the covariate balance aggregating all time strata and on the Love plot.

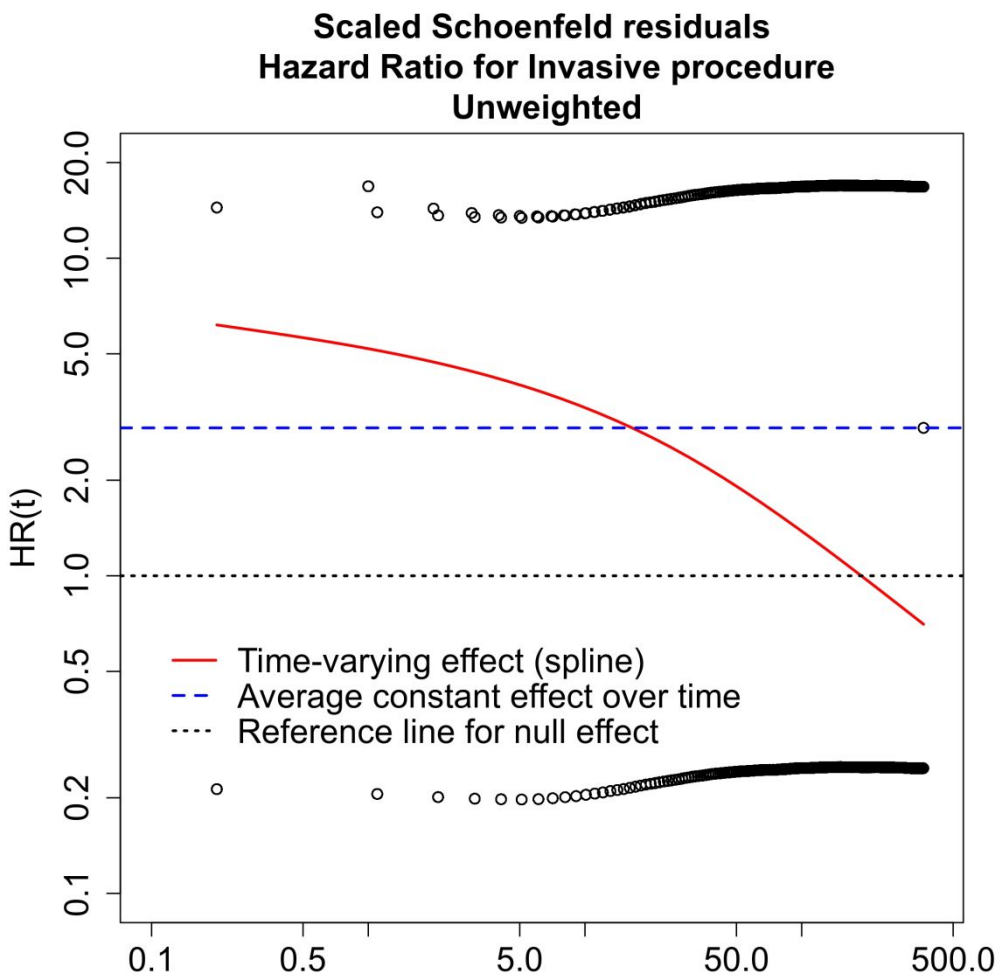
Figure S3: Density plots of daily SAPS-II along the first 3 days, according to invasive/conservative approach, before and after ATT weighting





The density plots shows that the distribution for SAPS-II (the major determinant of risk) along the first 3 days is higher in the invasive group before weighting, and is very much closer after weighting in the two groups.

Figure S4: Time-varying effect of invasive procedure at one year (Shoenfeld residuals / Modelization of time-varying effect)



The test of Schoenfeld residuals for proportional hazards assumption was significant, as the HR was decreasing along time, and was not significantly different from unity after 50 days

TABLES

Table S1: Association of Baseline Factors with death at one year (Cox model)

	Distribution		Univariate			Multivariate		
Variable	**Living at d365**	**Dead at d365**	**HR**	**95 % conf.int**	**P-value**	**HR**	**95 % conf.int**	**P-value**
Age (y)	84.3, 84 (82 - 86)	84.9, 84 (82 - 87)	1.03	[1.02, 1.03]	<0.001	1.04	[1.04, 1.05]	<0.001
Age [80-84]	27932 (58.1)	30949 (52.5)	1					
Age [85-89]	15841 (33)	21043 (35.7)	1.13	[1.11, 1.15]	<0.001	0.99	[0.96, 1.02]	0.510
Age [90+]	4286 (8.9)	6963 (11.8)	1.29	[1.26, 1.32]	<0.001	0.98	[0.92, 1.05]	0.601
Sex female	25524 (53.1)	28033 (47.5)	0.88	[0.87, 0.90]	<0.001	0.90	[0.88, 0.91]	<0.001
From Home	42819 (89.1)	51916 (88.1)	0.96	[0.94, 0.98]	0.001	0.93	[0.91, 0.96]	<0.001
Reason for admission : CardioVascular	16514 (34.4)	23675 (40.2)	1.28	[1.26, 1.30]	<0.001	1.42	[1.39, 1.46]	<0.001
Reason for admission : Respiratory	12617 (26.3)	17309 (29.4)	1.04	[1.02, 1.06]	<0.001	1.20	[1.17, 1.22]	<0.001
SAPS II	41, 38 (30 - 49)	57.9, 54 (40 - 73)	1.04	[1.04, 1.04]	<0.001	1.04	[1.04, 1.04]	<0.001
SAPS II [1-34[	17288 (36)	7913 (13.4)	1			1		
SAPS II [34-45[	14852 (30.9)	12264 (20.8)	1.58	[1.54, 1.62]	<0.001	1.01	[0.98, 1.04]	0.466
SAPS II [45-63[	11250 (23.4)	16677 (28.3)	2.49	[2.43, 2.55]	<0.001	0.95	[0.91, 1.00]	0.029
SAPS II [63-156]	4669 (9.7)	22101 (37.5)	6.18	[6.02, 6.34]	<0.001	0.89	[0.82, 0.95]	0.001
Charlson Comorbidity Index	2.3, 2 (1 - 3)	2.9, 2 (1 - 4)	1.04	[1.04, 1.05]	<0.001	1.05	[1.04, 1.06]	<0.001
Charlson CI = 0	11735 (24.4)	12237 (20.8)	1			1		
Charlson CI = 1	9793 (20.4)	9606 (16.3)	0.89	[0.87, 0.92]	<0.001	0.90	[0.87, 0.93]	<0.001
Charlson CI = 2-3	14821 (30.8)	17918 (30.4)	1.02	[0.99, 1.04]	0.130	0.97	[0.93, 1.00]	0.078
Charlson CI >= 4	11710 (24.4)	19194 (32.6)	1.18	[1.16, 1.21]	<0.001	1.01	[0.95, 1.07]	0.751
Charlson CardioVascular comorbidity	17654 (36.7)	22005 (37.3)	0.97	[0.96, 0.99]	<0.001	0.93	[0.91, 0.96]	<0.001
Charlson Respiratory comorbidity	14013 (29.2)	17794 (30.2)	0.97	[0.95, 0.98]	<0.001	0.98	[0.96, 1.01]	0.138
Charlson Kidney comorbidity	11648 (24.2)	16696 (28.3)	1.08	[1.06, 1.10]	<0.001	0.87	[0.85, 0.90]	<0.001
Charlson Neurologic comorbidity	4758 (9.9)	7304 (12.4)	1.17	[1.14, 1.20]	<0.001	1.00	[0.97, 1.04]	0.871
Charlson Dementia comorbidity	4083 (8.5)	6568 (11.1)	1.18	[1.15, 1.21]	<0.001	1.04	[1.01, 1.07]	0.010
Charlson Diabetic comorbidity	7109 (14.8)	9082 (15.4)	0.99	[0.97, 1.02]	0.578	0.84	[0.81, 0.86]	<0.001
Charlson OncoHaematologic comorbidity	6857 (14.3)	12305 (20.9)	1.27	[1.25, 1.29]	<0.001	0.99	[0.96, 1.03]	0.590
Year 2013	7945 (16.5)	9193 (15.6)	1			1		
Year 2014	7839 (16.3)	9645 (16.4)	1.04	[1.01, 1.07]	0.003	1.03	[1.00, 1.07]	0.029
Year 2015	8328 (17.3)	9958 (16.9)	1.03	[1.00, 1.06]	0.031	1.00	[0.97, 1.03]	0.949
Year 2016	8137 (16.9)	10175 (17.3)	1.06	[1.03, 1.09]	<0.001	1.00	[0.97, 1.04]	0.835

Year 2017	8041 (16.7)	10243 (17.4)	1.08	[1.05, 1.11]	<0.001	1.00	[0.97, 1.03]	0.933
Year 2018	7769 (16.2)	9741 (16.5)	1.07	[1.04, 1.10]	<0.001	0.98	[0.95, 1.01]	0.193
Universitary Hospital	12992 (27)	15402 (26.1)	1			1		
Private Hospital	9179 (19.1)	8232 (14)	0.76	[0.74, 0.78]	<0.001	1.15	[1.10, 1.20]	<0.001
Public Hospital	25888 (53.9)	35321 (59.9)	1.08	[1.06, 1.10]	<0.001	1.09	[1.07, 1.12]	<0.001
1st ICU Continuous monitoring	9084 (18.9)	6007 (10.2)	1			1		
1st ICU Intermediate	3290 (6.8)	1534 (2.6)	0.76	[0.72, 0.80]	<0.001	0.84	[0.79, 0.88]	<0.001
1st ICU Ressucitation	35685 (74.3)	51414 (87.2)	1.95	[1.90, 1.99]	<0.001	1.18	[1.14, 1.21]	<0.001
Hospital with Geriatric Unit	33848 (70.4)	45125 (76.5)	1.31	[1.28, 1.33]	<0.001	1.10	[1.06, 1.13]	<0.001
Hospital with Palliative Unit	25803 (53.7)	35287 (59.9)	1.23	[1.21, 1.25]	<0.001	1.01	[0.98, 1.03]	0.638

This table presents which baseline-factors are associated with death at one year in univariate and multivariate survival analysis. As expected, SAPS II showed the higher association with death.

Table S2: CCAM Codes of invasive procedures

Support	Code	French label	Translation
Ventilation	**GLLD004**	Ventilation mécanique intratrachéale avec pression expiratoire positive [PEP] supérieure à 6 et/ou FiO2 supérieure à 60%, avec technique de décubitus ventral alterné par 24 heures	Intratracheal mechanical ventilation with Positive End Expiratory Pressure [PEEP] greater than 6 and/or FiO2 greater than 60%, with alternating prone position technique per 24 hours
	GLLD008	Ventilation mécanique intratrachéale avec pression expiratoire positive [PEP] supérieure à 6 et/ou FiO2 supérieure à 60%, par 24 heures	Intratracheal mechanical ventilation with Positive End Expiratory Pressure [PEEP] greater than 6 and/or FiO2 greater than 60%, per 24 hours
	GLLD015	Ventilation mécanique intratrachéale avec pression expiratoire positive [PEP] inférieure ou égale à 6 et FiO2 inférieure ou égale à 60%, par 24 heures	Intratracheal mechanical ventilation with Positive End Expiratory Pressure [PEEP] less than or equal to 6 and FiO2 less than or equal to 60%, per 24 hours
Circulation	**EQLF001**	Injection intraveineuse continue de dobutamine ou de dopamine à débit inférieur à 8 microgrammes par kilogramme par minute [µg/kg/min], ou de dopexamine en dehors de la période néonatale, par 24 heures	Continuous intravenous infusion of dobutamine or dopamine at a dose less than 8 micrograms per kilogram per minute [µg/kg/min], or dopexamine outside the neonatal period, per 24 hours
	EQLF003	Injection intraveineuse continue de dobutamine ou de dopamine à débit supérieur à 8 microgrammes par kilogramme par minute [µg/kg/min], d'adrénaline ou de noradrénaline en dehors de la période néonatale, par 24 heures	Continuous intravenous infusion of dobutamine or dopamine at a dose greater than 8 micrograms per kilogram per minute [µg/kg/min], epinephrine or norepinephrine outside the neonatal period, per 24 hours

CCAM = the Classification Commune des Actes Médicaux is the common French Social Security classification of all medical procedures

REFERENCES

1. Scailteux LM, Droitcourt C, Balusson F, et al. French administrative health care database (SNDS): The value of its enrichment. *Therapie* 2019; **74:** 215–223.

2. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017; **26:** 954–962.

3. Fassier T, Duclos A, Abbas-Chorfa F, et al. Elderly patients hospitalized in the ICU in France: a population-based study using secondary data from the national hospital discharge database. *J Eval Clin Pract* 2016; **22:** 378–386.

4. Laporte L, Hermetet C, Jouan Y, et al. Ten-year trends in intensive care admissions for respiratory infections in the elderly. *Ann Intensive Care* 2018; **8:** 84.

5. Atramont A, Lindecker-Cournil V, Rudant J, et al. Association of Age With Short-term and Long-term Mortality Among Patients Discharged From Intensive Care Units in France. *JAMA Netw Open* 2019; **2:** e193215.

6. Cooke CR, Iwashyna TJ. Using existing data to address important clinical questions in critical care. *Crit Care Med* 2013; **41:** 886–896.

7. Black N, Payne M. Directory of clinical databases: improving and promoting their use. *Qual Saf Health Care* 2003; **12:** 348–352.

8. Hua M, Gershengorn HB, Wunsch H. Assessing delivery of mechanical ventilation: risks and benefits of large databases. *Intensive Care Med* 2020; 1–4.

9. Ettelt S, Nolte E. Funding Intensive Care - Approaches in Systems Using Diagnosis-Related Groups. *Rand Health Q* 2012; **1:** 7.

10. Busse R, Geissler A, Aaviksoo A, et al. Diagnosis related groups in Europe: moving towards transparency, efficiency, and quality in hospitals? *BMJ* 2013; **346:** f3197.

11. Didier R, Gouysse M, Eltchaninoff H, et al. Successful linkage of French large-scale national registry populations to national reimbursement data: Improved data completeness and minimized loss to follow-up. *Arch Cardiovasc Dis* 2020; **113:** 534–541.

12. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique* 2017; **65:** S149–S167.

13. Trombert-Paviot B, Rector A, Baud R, et al. The development of CCAM: the new French coding system of clinical procedures. *Health Inf Manag J Health Inf Manag Assoc Aust* 2003; **31:** 1–11.

14. Bittner MI, Donnelly M, van Zanten AR, et al. How is intensive care reimbursed? A review of eight European countries. *Ann Intensive Care* 2013; **3:** 37.

15. ATIH : Agence technique de l'information sur l'hospitalisation. 2022. https://www.atih.sante.fr/

16. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. *Springer New York* 2000; doi:10.1007/978-1-4757-3294-8

17. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. *Stat Med* 2009; **28:** 2473–2489.

18. Royston P, Parmar MKB. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med* 2011; **30:** 2409–2421.

19. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. *J Clin Oncol Off J Am Soc Clin Oncol* 2014; **32:** 2380–2385.

20. Grafféo N, Latouche A, Geskus RB, Chevret S. Modeling time-varying exposure using inverse probability of treatment weights. *Biom J Biom Z* 2018; **60:** 323–332.

21. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014; **33:** 1242–1258.

22. Wyss R, Gagne JJ, Zhao Y, et al. Use of Time-Dependent Propensity Scores to Adjust Hazard Ratio Estimates in Cohort Studies with Differential Depletion of Susceptibles. *Epidemiol Camb Mass* 2020; **31:** 82–89.

23. Hernán MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med* 2002; **21:** 1689–1709.

24. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. *Stat Methods Med Res* 2017; **26:** 1654–1670.

25. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Stat Med* 2014; **33:**1685–1699.

26. Austin PC, Thomas N, Rubin DB. Covariate-adjusted survival analyses in propensity-score matched samples: Imputing potential time-to-event outcomes. *Stat Methods Med Res* 2020; **29:** 728–751.

Comparison of conservative and invasive approaches on one-year survival among critically ill elderly medical patients: nationwide observational study

(The OCTO-REVERSE Study)

STATISTICAL ANALYSIS PLAN

Version 1: December 2, 2019
Version 2: August 5, 2021
Reformatting for publication: 2023

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INTRODUCTION

SAP version and revision story

The statistical analysis plan was developed during the summer of 2021 during data collection (in two meetings: June 10, 2021, and August 5, 2021, with numerous exchanges in between), before having full access to the study database.

It was structured as an extension of the scientific protocol (also attached, drafted in French on December 2, 2019, which is actually the first version of the statistical analysis plan). The main differences between these two versions are:

- The exclusion of renal replacement therapy as a variable of interest (due to coding biases between acute and chronic situations)
- The enhanced statistical evaluation, specifically considering Time-to-Event analyses, with the collaboration of Philippe Aegerter, as senior statistician.

The current document was written after accessing the database and analyzing the data, it has been drawn up in accordance with the guidelines provided by the study: *Hiemstra B, Keus F, Wetterslev J et al. DEBATE-statistical analysis plans for observational studies. BMC Med Res Methodol 19, 233 (2019). https://doi.org/10.1186/s12874-019-0879-5*

We certify that this SAP is adequate in scope of the main analyses of the Octo-Reverse study.

Project number and human subjects protection review boards

- Local project number (scientific protocol) : Committee of Expertise for Research, Studies, and Evaluations in the Health Field: **CEREES Registration: 962976** (April 23, 2020)
- Independent national data protection authority: **CNIL Registration: 920181** (May 11, 2020)
- Independent institutional review board: **IRB Registration: #00011928** (August 19, 2022)

Background and rationale

The Covid-19 pandemic highlighted older age as a strong factor associated with death, raising again the question of the relevance of critical care for elderly patients. Regardless of the pandemic, the heterogeneity of studies on this issue brought one-year survival rate after intensive care unit (ICU) admission to about 50% for older patients. This absolute uncertainty could have favored decision-making process based on clinical judgment alone while triage-systems based even on limited evidence would have been ethically preferable. In addition, overoptimistic expectations of outcome could have favored the increasing proportion of elderly patients admitted to ICU and the enhancement of time-limited trial approach for invasive treatments, which a part turned out to be disproportionate. After correcting for the growing frailty that accompanies aging, those studies showed main factors of poor prognosis: older age (≥ 80 years), non-operative condition and exposition to an invasive procedure. By performing a nationwide study, we will seek to assess characteristics, management and outcomes for elderly-ICU patients after the combination of these three factors.

METHOD

Research hypothesis

The null hypothesis is that there is no true association between any single use or a combination of invasive procedures (invasive approach vs, on the contrary, conservatice approach) and prognosis of older patients admitted for medical reason in ICUs.

The alternative hypothesis is that there is an association between invasive approach and prognosis.

Study objectives

The primary objective of this study is to determine the association between the use of an invasive procedure during the ICU stay and one-year survival starting from the date of ICU admission.

Secondary objectives are to explore the association between the use of an invasive procedure during the ICU stay and:

- Overall Mortality Rate at 28, 90 and 365 days
- Overall Mortality Rate in ICU and in hospital
- Length of ICU stay and hospital stay
- ICU readmission rate at one year

Study design

The Octo-Reverse study is a retrospective analysis of data prospectively collected in the Système National des Données de Santé (SNDS), the national French healthcare database. The entire study is purely observational in design; no interventions were applied as part of the study protocol.

Sampling

Being an observational study, there is no randomization of patients. All patients and stays responding to selection criteria were used without

Framework

All outcomes are tested for superiority

Sample size, power and detectable association

Previous studies examining the prognosis of very old patients in the ICU have shown variability across different countries, settings, selection criteria, analyzed factors, and time horizons. Few studies specifically addressed the impact of invasive procedures. Of particular relevance is the study by Atramont et al. which investigated 2013 French ICU patients and calculated odds ratios (OR) for in-hospital death associated with invasive mechanical ventilation (2.42; 95% CI [2.25-2.62]) and vasopressor support (2.63; 95% CI [2.45,2.83]), while the ORs for 3-month mortality after hospital discharge were much lower (1.08 [0.97-1.21] and 1.30 [1.16-1.45], respectively). Similarly, Ferrante et al. reported in their 1998-2012 US monocentric study that mechanical ventilation was strongly associated with 1-year mortality (adjusted Hazard Ratio, 2.89; 95% CI [1.91-4.37]).

During the year 2013, Atramont identified 23,283 patients aged 80 or older, with nearly 45% being surgical (including trauma and burn injuries) patients, resulting in approximately 10,000 patients per year. However, intermediate and step-down units were not included in their analysis. Among these older patients, approximately 56% received mechanical ventilation. Mortality rates were 30.4% and 61.7% for in-hospital and 3-year post-discharge, respectively. Fassier et al. reported an in-hospital mortality rate of 33.9% among the 32,844 French ICU hospitalizations in 2009, while the monocentric study by Roch et al. found a higher rate of 55%. Seethala et al. reported a 1-year mortality rate of 32.8% among 10,583 US patients, whereas Roch (15) found a rate of 72%.

For our study, we anticipate including at least 15,000 patients each year. Our main analysis will focus on mechanical ventilation as an example for our power calculation. Assuming that the 1-year mortality rate among controls ranges from 0.3 to 0.5, and the risk ratio associated with this procedure is at least 1.1, a global sample size of 3200 (for a mortality rate of 0.5) to 7600 (for a mortality rate of 0.3) will provide 80% power to detect this effect. Additionally, patient matching based on propensity score will increase power. Lastly, as we are interested in potential trends in patient trajectories, our dataset will encompass multiple years.

Timing of final analyses

Data cleansing will be performed upon retrieval of the selected dataset. The final analysis will be conducted hereafter.

Timing of outcome assessment

Death certificates are continuously collected by Cepi-DC, using an automated procedure, followed by checks. The coding of causes of deaths is made by experts, so the detailed update of the SNDS database is within 6 to 12 months.

In our dataset, follow-up of patients without a death record will be censored at a date corresponding to the 95th percentile of all dates of death.

STATISTICAL PRINCIPLES

Confidence interval and p-values

In this prognostic study, there is a single primary outcome, and therefore, no adjustment will be made for multiplicity. For the secondary objectives, all relevant statistical tests will be two-sided and conducted at a significance level of 0.05. Additionally, all reported confidence intervals will be 95% and two-sided.

Adherence and Protocol deviations

As the study is strictly observationnal and aims to summarise what is the “real life” of older patients in ICUs, protocol deviations are not applicable.

Analysis sets

The analysis population is defined based on the recorded ICU procedures in the database. This means that the individuals included in the analysis sets are defined “as treated” and selected according to the specific treatments and interventions they received during their ICU stay, as documented in the database.

STUDY POPULATION

Screening and eligibility

Eligible patients who were not included will be compared to included patients by comparing their general characteristics (age, sex, year of admission), and SAPS-II scores. All eligible patients will be included on their first day of ICU admission, whatever the duration of the ICU stay or the level or the ICU (intermediate or step-down unit).

Inclusion criteria

- Age at ICU admission ≥ 80 years
- ICU admission during the period January 2013- December 2018
- Non-operative condition, defined as no surgical procedure or no surgical DRG, either during the hospitalization encompassing the index ICU stay or during the 30 days before this ICU admission

Exclusion criteria

Any of the following:

- Any missing data on the following core dataset : age, sex, SAPSII, main diagnosis, procedures (code and timing), dates (admission, discharge, follow-up), DRG code
- DRG error

Data Retrieval

During the preparation of this SAP, the retrieval of data was still in progress. To comply with our request and French regulations on data confidentiality, the SNDS data managers have deposited a subset of the entire database into a dedicated secure workspace. This subset specifically includes individuals who were admitted to an intensive care unit (including intermediate and step-down units) at least once between 2009 and 2018 and were aged 80 or above at the time of admission.

Given the structure of the database, the following steps are necessary:

- Removal of hospital stays with erroneous DRG codes, utilizing a key that combines the year of discharge, hospital code, and stay code within the hospital and year.
- Concatenation of hospital stays for the same patient across time, organizing them by entry date and calculation of the time interval between successive stays.
- Association of each hospital stay with its corresponding elementary stays in different units to generate an array of unit stays, ordered by entry time in a wide format.
- Calculation of the duration of each unit stay, particularly in the ICU.
- Linkage of the table of procedures (including procedure codes, number of executions, and start and stop dates within the hospital stay) to the table of hospital stays using the stay key, resulting in an array of procedures ordered by their start time in a wide format.
- Identification of hospital stays with surgical procedures.
- Determination of the unit where each procedure was performed.
- Calculation of the start time and total duration of invasive procedures (such as invasive ventilation and vasopressor support) within the ICUs.
- Connection of the table of secondary diagnoses (ICM10 codes) to the table of hospital stays using the stay key to obtain an array of ICM10 codes, ordered by the units where they were attributed.
- Linkage of the table of hospitals (including information on public/private funding, university status, equipment, geriatric or palliative care facilities) to the table of hospital stays using the hospital code.
- Association of the resulting table of documented stays with the table of patients to retrieve social insurance status, date, and cause of death.
- To ensure homogeneity, exclusion of the years 2009-2012 due to modifications in the structure of some tables or the recording of SAPSII.
- Chronological arrangement of the stays, and selection of the first hospital stay where each patient was admitted to an ICU for non-surgical reasons, provided they were 80 years or older.

A STROBE flow diagram will be used to illustrate the progression of patients throughout the study, from the initial screening for eligibility in the database to the partitioning based on ICU procedures and the one-year follow-up. Additionally, we will summarize the number of exclusions, along with the reasons for their exclusion.

Withdrawal or lost to follow-up

The study is a retrospective analysis of data already collected in the SNDS. Recording of hospitalization data is mandatory in the SNDS. Therefore, the concept of withdrawal or lost for follow-up cannot be applied.

Baseline characteristics

The following information will be collected at the time of ICU admission:

- Age (in years)
- Gender
- Social status and place of residence
- Simplified Acute Physiology Score (SAPS) II at ICU admission
- Pre-existing medical conditions and diagnoses (which will be used to calculate the Charlson's comorbidity score)
- Reason for ICU admission
- Dates of hospital and ICU admission
- Pre-admission location (such as home, emergency department, another unit, or another hospital)
- Characteristics of the hospital and ICU (funding, university affiliation, level of care)

We will present these characteristics in a baseline characteristics table. Continuous variables will be summarized using either the mean and standard deviation (SD) or the median and interquartile range (IQR) for variables with asymmetric distribution. The normality of continuous data will be assessed through Q-Q plots and histograms. Categorical variables will be described by the proportion of participants in each category, along with 95% confidence intervals (CIs) when applicable.

ICU daily follow-up

- Vital status
- Hospital and ICU discharge or readmission (date, pre-admission location: home / emergency / other unit / other hospital, destination: home / other unit / other acute hospital / long-term care)
- Endotracheal intubation, extubation, re-intubation, tracheostomy
- Life-sustaining treatments. These procedures are date-stamped (relative to the start of the hospital stay) and coded using a national multidimensional classification system called CCAM
- Main diagnosis and secondary diagnoses (ICM10)

Long term follow-up

- Readmission to the hospital or ICU
- Vital status
- Causes of death, if applicable

We will extract mortality data at 30 days, 3 months, 1 year, and 5 years from the survival duration. Additionally, we will present the length of ICU and hospital stay, as well as readmission rates at one year

Exposure

The exposure variable will be defined as the first occurrence of either vasopressor support or invasive mechanical ventilation during the ICU stay. This will be referred to as the invasive approach, while the opposite will be referred to as the conservative approach. We make this choice because these procedures are reliably documented for urgent decision-making. We will not consider non-invasive ventilation and renal replacement therapy due to the ambiguity in coding between acute and chronic situations, and sometimes maintained as palliative support.

Assumed confounding covariates

The majority of variables measured in our study are inherently correlated, as they primarily pertain to a patient's physiological reserve or functional status. Unmeasured factors, such as environmental, genetic, or psychological influences, have the potential to confound our outcome variables. To address this, we provide an illustrative example of confounding variables and categorize them as either 'measured' or 'unmeasured'.

Mortality is presumed to be confounded by:

- Measured: age, sex, pre-existing comorbidities (Charlson), SAPS-II score, reason for admission, palliative care, preadmission location, and ICU or hospital characteristics (academic status)
- Unmeasured: respiratory and circulatory parameters, cause of mortality (e.g., death resulting from multi-organ failure, failure to rescue, do-not-resuscitate [DNR] orders, patient's or family's personal wishes, or a combination thereof), crowding or insufficient caregiver availability, ICU or hospital characteristics.

Length of stay is presumed to be confounded by:

- Measured: age, comorbidities (Charlson), SAPS-II score, palliative care, ICU or hospital characteristics
- Unmeasured: crowding or insufficient caregiver availability, ICU or hospital characteristics.

Hence, we acknowledge the presence of residual confounding in our dataset due to unmeasured confounding factors, some of which have been outlined above

ANALYSIS

Descriptive

All continuous variables, including changes from baseline, will be summarized globally and according to the ICU approach (invasive vs conservative) using means, standard deviations (SD), or medians and interquartile ranges for skewed variables. Categorical variables will be summarized globally and according to the ICU approach using counts and percentages, supplemented with 95% confidence intervals (CIs). The normality of distributions for quantitative variables will be assessed using Q-Q plots and histograms. For each variable, unless otherwise specified in advance, the choice of statistical tests and multivariate models (parametric or non-parametric) will be determined based on observed characteristics such as the normality of distributions and residuals, as well as collinearity. The relationship between a quantitative factor and any response will be explored by fitting fractional polynomials.

Primary end-point and time-to-event analysis

- Measurement of Survival and Follow-up

Survival will be assessed from the date of ICU admission until the date of death or until the last follow-up, in cases where the patient's data is no longer available. Since the data refreshment for SNDS (French healthcare data system) occurs periodically nationwide, the date of the last follow-up will be estimated using the 95th percentile of the recorded dates of death.

- Comparison of Mortality Proportions

The raw mortality rates at one year will be compared between the two ICU approaches using a Chi-squared test.

- Time-to-Event Analysis

The main comparison will be analyzed using a time-to-event approach, with a censoring time set at one year (365 days) from the first ICU admission. The description of mortality proportions will be presented using Kaplan-Meier survival curves when independent factors are binary (such as ICU approach or procedures), categorical (pre-admission location), or ordinal (either native, like the Charlson index, or resulting from dividing a continuous variable into groups, such as age groups).

- Immortal Time Bias

To address the issue of immortal time bias when comparing the survival of the invasive group (patients receiving vasopressor support or invasive mechanical ventilation) with the conservative group, the occurrence of an invasive procedure will be considered as a time-dependent covariate. The time of first use of any invasive procedure will be estimated and treated as a covariate in the analysis. To avoid ties, when the first invasive procedure and death occur on the same day, the time of death will be shifted by 0.1 day. Time-dependent Kaplan-Meier survival curves will be established following the approach proposed by *Steven M Snapinn, Qi Jiang & Boris Iglewicz (2005) Illustrating the Impact of a Time-Varying Covariate With an Extended Kaplan-Meier Estimator, The American Statistician, 59:4, 301-307, DOI: 10.1198/000313005X70371*

- Univariable Cox Proportional Hazard Regression Analysis

Associations between the incidence of death at one year and exposure or confounding factors will be explored using univariable Cox proportional hazard regression analysis. The relationship between a quantitative factor and the incidence of death will be examined by fitting fractional polynomials.

- Multivariable Analysis

Covariates with a p-value less than 0.2 in the univariable analysis will be included in the multivariable model. A multivariable analysis of the association between procedures or patient characteristics and outcomes will be performed using a Cox proportional hazards model. Hazard ratios (HR) will be calculated, and ties will be handled using the Efron approximation. The proportional hazards assumption will be assessed through plots of scaled Schoenfeld residuals and corresponding tests. If a time-varying effect is detected, the Cox model will be extended by adding an interaction term between the covariate and a transformation of time, with the choice of transformation determined by the Akaike Information Criterion (AIC).

- Propensity Score Analysis

Given the potential differences between patients receiving invasive support and those in the conservative group, a propensity score (PS) method will be employed to minimize confounding and obtain an unbiased estimate of the treatment effect. However, conventional PS methods may introduce bias when treatment or exposure varies over time. To address this issue, an inverse probability of treatment weighting (IPTW) method adapted to the time-dependent context will be used. The time span will be divided into strata, allowing the calculation of a propensity score at different time points. Propensity scores will be calculated using a Cox model that predicts the use of invasive procedures based on patient characteristics available at admission. Emphasis will be placed on balancing prognostically important covariates in the score.

- Validation of Propensity Score Weighting

Propensity score distributions will be examined to assess the overlap between the two groups before and after weighting. Variable balance will be assessed by examining standardized mean differences before and after weighting, variance ratios between the two groups, and the overlapping coefficient. Sensitivity analyses will be conducted by trimming weights at different percentiles.

- Estimation of Treatment Effects

IPTW will be used to estimate the average treatment effect (ATE) for the 1-year mortality associated with invasive support compared to the conservative approach. Hazard ratios (HR) and their 95% confidence intervals will be estimated. As weighting may modify the sample size relative to the original population and induce a lack of independence, a robust sandwich-type estimator will be used to calculate standard errors, accounting for this uncertainty. Regression adjustment will also be employed to address confounding variables used for stabilization.

- Summary of Results

When the treatment effect is time-varying, the overall hazard ratio (HR) will be interpreted as a weighted average HR over the event times. Additionally, the difference in the restricted mean survival time (RMST) will be calculated as a model-free parameter, providing a measure of the loss of life expectancy.

Sensitivity and subgroup analyses

We will conduct sensitivity analyses to evaluate the reliability of the overall hazard ratio (HR) associated with invasive procedures. These analyses will involve the following approaches:

- Trimming of ATT Weights: We will assess the impact of different trimming methods on the results. Specifically, we will examine the HR using propensity score weights that are trimmed at the 5th and 95th percentiles, as well as without any trimming.

- Time Strata Definition: The robustness of the results will be examined by defining time strata based on different criteria. We will consider time strata where each day an invasive procedure or a death occurred, as well as predefined periods.

In addition to the sensitivity analyses, the interpretation of the results will be enhanced by analyzing mortality at various follow-up times. We will assess mortality rates at 28 days from ICU admission, at one year from hospital discharge, as well as at 7 and 30 days.

Regarding subgroup analysis, we will divide the population into three subcohorts based on age: less than 85 years, 85 to less than 90 years, and 90 years or older. A Forest plot will be generated, presenting the estimated point and confidence intervals for the treatment effect across these age subgroups.

Secondary End-points

The secondary survival endpoints will be described and analyzed using the same methodology as the primary endpoint.

For the readmission rate, the data will be modeled as time-to-event, censored at 365 days (D365), within a competing risk framework. In this framework, readmission will be considered the main event, while death before readmission will be treated as a competing event. The time to each event, referred to as subdistribution hazards, will be modeled using a Fine & Gray model, with the type of ICU approach (invasive or conservative) included as a covariate. This analysis will provide a subdistribution hazard ratio (SHR), which takes into account both the time to readmission and the probability of death. Additionally, the length of ICU stay (in days) and the length of hospital stay will be compared between the two ICU approaches using a Wilcoxon test. These lengths will also be modeled using a linear model.

Missing Data

Since stays with any missing data on the core dataset will be excluded from the analysis, there is no need for imputation of missing data.

[Statistical software : All statistical analyses will be conducted using the SAS Enterprise Guide v7.15 (SAS Institute Inc., Cary, NC, USA) provided by the SNDS infrastructure].

BMJ Open

Conservative compared with invasive approaches and one-year survival among critically ill elderly medical patients (OCTO-REVERSE Study): a nationwide observational study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-089835.R1
Article Type:	Original research
Date Submitted by the Author:	25-Mar-2025
Complete List of Authors:	LECLAIRE, Clement; Assistance Publique - Hopitaux de Paris, Paris Public Hospital at Home (HAD AP-HP), Greater Paris University Hospitals GEORGES, Alexandre; Assistance Publique - Hopitaux de Paris, Paris Public Hospital at Home (HAD AP-HP), Greater Paris University Hospitals de stampa, matthieu; CESP, Inserm U1018, Center for Research in Epidemiology and Population Health (CESP), University of Versailles Saint-Quentin-en-Yvelines (UVSQ); Centre Gerontologique Departemental, Departmental Gerontological Center, Marseille Aegerter, Philippe; CESP, Inserm U1018, Center for Research in Epidemiology and Population Health (CESP), University of Versailles Saint-Quentin-en-Yvelines (UVSQ)
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Ethics, Geriatric medicine, Palliative care, Patient-centred medicine
Keywords:	PALLIATIVE CARE, Triage, Person-Centered Care, Caregivers, INTENSIVE & CRITICAL CARE, Health Services for the Aged

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Conservative compared with invasive approaches and one-year survival among critically ill elderly medical patients (OCTO-REVERSE Study): a nationwide observational study

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Manuscript word count: 4202

ABSTRACT

Objective: To determine whether an invasive approach is associated with favourable long-term outcomes among elderly medical patients in the ICU, compared to a conservative approach.

Design: Nationwide observational study (OCTO-REVERSE Study) using data prospectively collected in the National French Healthcare Database (covering 99% of the population, 66 million people).

Setting: Comprehensive multicentre study through the linkage of large-scale national registries (including all public or private facilities) from 2013 to 2018 to avoid ambiguities related to the COVID-19 pandemic.

Participants: All nonsurgical patients aged 80 years or older admitted to an ICU in France during the period (n=107 014 patients at 822 hospitals).

Outcome measures: The main outcome was the one-year survival rate. The association of the two approaches with one-year survival was estimated using a time-dependent Cox model and a propensity score adapted to time-to-event analysis, yielding the average treatment effect in the treated (ATT) and extended weighted Kaplan Meier curves.

Results: 107 014 patients were categorized into two groups based on the type of care received: invasive (n=51 680 [48%] received invasive ventilation and/or vasopressor support) or conservative (n=55 334 [52%] received neither). One-year survival rate was significantly lower in the invasive group than in the conservative group (27% vs 59% estimated with extended time-dependent Kaplan Meier method). The risk of death in the invasive group remained significantly higher after time-dependent propensity score (PS) weighting (hazard ratio, 1.64; 95% CI, 1.60-1.69, p<0.001). The loss in restricted mean survival time (RMST) was 67.7 days (95% CI, 65.7-69.8) in this group and 31% of deaths occurred the day of initiation of the procedure, or the following day.

Conclusion: Among the whole population of critically ill elderly medical patients in France, the invasive approach was unknowingly associated with end-of-life care in nearly three-quarters of cases. Further research is needed to align intensive care with compassionate goals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study uses the National French Healthcare Database, which records all medical procedures coded for reimbursement, ensuring exhaustiveness and real-world representativeness.
- This study employs a robust time-dependent analysis using the extended Kaplan-Meier method, which accounts for variations in treatment exposure over time and improves survival estimates.
- The SAPS II, used in the propensity score model as the main severity adjustment factor, proved to be the primary determinant in balancing patient characteristics between groups.
- The main limitation is the presence of potential unmeasured confounding factors, including key clinical parameters that could influence both treatment decisions and patient outcomes.
- Information on whether care was withheld or withdrawn is not available, making it difficult to assess the impact of end-of-life decisions on mortality differences.

INTRODUCTION

The proportion of older patients in the ICU has been steadily increasing over the past two decades, although the overall benefit to patient outcomes remains unclear.[1] Many studies have explored this topic, but variations in patient selection (age 65 to 90, surgical vs. medical, invasive vs. conservative care) and outcome measures (mortality vs. functional status, early vs. delayed assessment) have led to uncertain conclusions.[2] Additional research is needed to address the care consequences of this growing population. However, a randomized trial has been deemed infeasible on ethical grounds.[3] The ensuing uncertainty may have led to a decision-making process based solely on clinical judgment, while triage-systems based on even limited evidence would have been preferable.[4] In addition, over-optimistic expectations[5] of outcomes could have favoured the expansion of time-limited trials,[6] some of which turned out to be disproportionate. Previous studies on this issue[7–9]

have identified older age (≥80 years),[10] non-operative condition,[11] and exposure to invasive procedures (primarily invasive mechanical ventilation and vasopressor therapy)[12–14] as prognostic factors that should be considered especially as to long-term outcomes. By conducting a nationwide study that combines these three factors, we aimed to assess the characteristics, management, and one-year survival of the entire target population of elderly patients admitted to the ICU for medical reasons in France.

METHODS

Study design and data sources

We performed a nationwide retrospective analysis (OCTO-REVERSE Study) using data prospectively collected in the Système National des Données de Santé (SNDS), the national French healthcare database that covers 99% of the population regardless of socioeconomic status (66 million). The SNDS was created for hospital payment and government purposes, and regular audits are conducted to ensure reliability and completeness. The SNDS also facilitates epidemiological research, with a specific interest in aging by an extended follow-up. Formal methods have been developed to assess the strengths and limitations of databases, and population-level data have enhanced our understanding of the use and outcomes of mechanical ventilation,[12] particularly for elderly patients hospitalized in ICUs in France.[15–17] The SNDS the national hospital discharge database of diagnosis-related groups (DRG) "PMSI," to the national death registry "CépiDC", enabling the tracking of individual patient trajectories following any hospital stay until death. This allows for the identification of the date and place of death, whether it occurs in hospital or in the community. It contains comprehensive medical and administrative data for all patients in the country. This linkage of large-scale French national registry populations contributes to guiding public decisions. Each patient is assigned a unique identification number with pseudonymized information, allowing individuals to be followed over time by linking inpatient and outpatient data from each hospitalization in all public or

private facilities in France. Procedures, including surgery or life-sustaining treatments, are time-stamped and coded using a national classification system called CCAM (**Supplementary Appendix 1**). The study was submitted to and approved by the independent national data protection authority (**CNIL Registration: 920181**). All data were deidentified for research purposes, and French law waives the need for informed consent. An independent institutional review board approved the study protocol (**IRB Registration: #00011928**).

Study population

All patients aged 80 years or older with complete data, admitted to hospitals in France from January 2013 through December 2018 (to avoid any ambiguities related to Covid-19), were eligible. We then selected ICU stays where the Simplified Acute Physiology Score (SAPS) II is comprehensively collected. To select the non-operative condition, we excluded stays that involved a surgery or whose DRG was surgical (or severe burn injury), either during the ICU stay or within 30 days prior to the ICU admission. To avoid counting multiple hospital outcomes for a single patient, only the first hospital stay including a medical admission to an ICU during the study period was considered for each patient, and readmission stays were excluded. Finally, we considered the invasive condition for patients who underwent invasive mechanical ventilation (CCAM codes GLLD004, GLLD008, GLLD015) or vasopressor support (CCAM codes EQLF001, EQLF003) (**Table S2 in Supplementary Appendix 1**).

Variables and exposure

The exposure variable was defined as the first occurrence of one of the following invasive procedures during the ICU stay: vasopressor support or invasive mechanical ventilation. We focused on these two main modifiable factors of interest because clinicians often question their benefit for the oldest patients. This choice was also driven by their coding reliability, as there is a clear-cut bedside decision without delay, marking a turning point in the patient's trajectory. We did not include non-invasive ventilation because its use as a palliative treatment for dyspnea has become increasingly common.

We also did not include renal replacement therapy due to the large grey area in coding between acute and chronic situations, and because its initiation can often be delayed without threatening the prognosis.[18] We addressed potential confounding resulting from variation in the case mix by controlling for age, severity of illness, pre-existing medical conditions expressed by the Charlson comorbidity index, primary diagnosis at admission, preadmission location, and academic status of the ICU. These confounders were specified a priori to develop a risk adjustment model for mortality. Patients were followed until death or the end of the year 2019, whichever occurred sooner. The invasive and non-invasive cohorts were mutually exclusive.

Outcomes

The primary objective of our analysis was to describe the one-year mortality of two populations of elderly medical ICU patients based on treatment intensity (invasive vs. conservative care). Additionally, we analysed intermediate mortality rates and lengths of stay, both in ICU and in hospital.

Statistical analysis

Characteristics of patients according to the use of invasive procedures were described using mean and standard deviation for age, and median and interquartile range (IQR) for other continuous variables. Categorical variables were presented as counts and percentages. Comparisons between the two groups were performed using the Wilcoxon test for continuous variables and the Chi-square test for categorical variables. Crude mortality rates were calculated at ICU and hospital discharge, along with one-year readmission rates and the duration of procedures and hospital stays, for both groups and for each invasive procedure (**Supplementary Appendix 2, pp. 11–12**).

Survival was measured from the date of ICU admission to the date of death or censored at the last follow-up. To limit immortal time bias, the occurrence of any invasive procedure was considered as a

time-dependent covariate. Time precision was day, and the time of death was shifted by 0.1 day to avoid ties with the time of the procedure. Multivariate analysis of survival was performed by a Cox proportional hazards (PH) model producing hazard ratios (HR). The handling of ties used the Efron approximation. The PH assumption was verified by scaled Schoenfeld residuals. The time-varying effect of a procedure was modelled by adding an interaction term between the corresponding covariate and some transformation of time. The restricted mean survival time (RMST) method was selected because it is not dependent on the number of events and on the assumption of proportional hazards, as is the case in time-to-event analyses. RMST reflects the life expectancy of patients up to a specified time. Details regarding the statistical methods are provided in **Supplementary Appendix 1**. As patients receiving invasive procedures may differ from the conservative ones, a propensity score (PS) was used to minimize the effects of confounding. Assumed confounders included age, sex, pre-existing comorbidities (Charlson Comorbidity Index), SAPS II score, year, reason for admission, availability of a palliative or geriatric care team in the hospital, pre-admission location, ICU level, and hospital characteristics (**Figure S2 and Table S1 in Supplementary Appendix 1**). However, the population at risk changes over time due to attrition (death or discharge). Therefore, we used an inverse probability of treatment weighting (IPTW) method adapted to the time-dependent context.[19] IPTW usually estimates the average effect of treatment when the entire sample is moved from control to treated (ATE). But this seemed unrealistic for invasive support in the elderly population, so here IPTW targeted the average treatment effect in the treated (ATT). We divided the time span into strata within which a distinct PS could be calculated. These strata were each day until day 14, then periods 14-20, 20-30, every 15 days until 120, and then every 30 days until 365 (case base). This time-stratified PS was built using a Cox model that predicted the use of invasive procedures by variables available at admission. The influence of continuous variables (age and SAPS II) was modelled by fractional polynomials (FP). Variable balance was assessed by examining the standardized mean differences before and after weighting. Weights were trimmed at the first and 99th percentiles. To remove residual confounding as much as possible, we combined weighting at the design stage with

regression adjustment on the same confounders (as listed in **Figure S2 and Table S1 in Supplementary Appendix 1**) at the analysis stage when estimating treatment effects.[20] A robust sandwich-type estimator was used to calculate standard errors.

We performed sensitivity analyses to assess the robustness of the overall HR associated with invasive procedures: initially by using ATT weights truncated at the 5th and the 95th percentiles, then by using time strata defined by every day an invasive procedure or death occurred.

All tests were two-sided, and a p-value < 0.05 was considered statistically significant. The analysis used the SAS Enterprise Guide v7.15 (SAS Institute Inc., Cary, NC, USA) provided by the SNDS infrastructure.

Patient and public involvement

None.

RESULTS

The final analysis included 107 014 first stays of patients aged 80 years or older who were admitted to an ICU for medical reasons at 822 hospitals, mostly publicly funded (65%), in France between 2013 and 2018. Among those patients, 51 680 (48%) received invasive ventilation or vasopressors, and 55 334 (52%) received neither of the two. A flowchart of patients and stays in the study is shown in **Figure 1**.

The demographic characteristics and the outcomes since ICU admission are shown in **Table 1**. The mean age was 84.6 years. More than half (52%) were male in the invasive group, and 52% were female in the conservative group. Overall, 89% were admitted from home, with most of them having a stop at the emergency department (59%). Patients in the invasive group had a significantly higher

severity of illness at admission as reflected by a higher SAPS II but fewer general coexisting conditions as reflected by a lower Charlson comorbidity index. Over the years, the flow of patients was increasingly directed towards the invasive group. Among 51 680 (48%) patients in the invasive group, 70% were dead at one year, while among 55 334 (52%) patients in the conservative group, 41% were dead at one year (Chi-square test, $p < 0.001$).

Outcomes of patients in the invasive group since ICU admission are detailed in **Table 2**. Among 38 427 patients who underwent vasopressors, 72% were dead at one year. Among 40 495 patients who received invasive ventilation, 72% were dead at one year. Patients who received a first invasive procedure were likely to receive the other one in 53% of cases, and one-year mortality was then 77%, whereas it was 60% and 63%, respectively, for vasopressors only or ventilation only. Among 8 761 patients who underwent renal replacement therapy (regardless of the group), 74% were dead at one year. The median number of days in the ICU was 4 (interquartile range 2 – 8). The median number of days in the hospital was 8 (interquartile range 2 – 16). The median duration of ventilation was 3 days (interquartile range 2 – 7). There were 2582 patients who underwent prone-positioning. In their case, the median number of sessions was 2 (interquartile range 1 – 3) per patient. The median duration of vasopressor support was 2 days (interquartile range 1 – 4). The time of the initial invasive procedure was the day of ICU admission for 79% of patients in the invasive group and the following day for an additional 9% (**Figure S1 in Supplementary Appendix 1**). More than half of the patients in the invasive group had both procedures, generally on the same day (86%). If vasopressors predated ventilation (6%) or ventilation predated vasopressors (9%), the median interval of initiation was 1 day (interquartile range 1 – 3). 24% of deaths in the invasive group occurred on the day of the initiation of any procedure, and 7% the following day.

After the calculation of the time-stratified PS, the balance obtained on ATT weighted samples was good, with absolute standardized differences less than 0.1 (**Figure S2 in Supplementary Appendix 1**).

The test of Schoenfeld residuals for the proportional hazards assumption was significant, as the HR was decreasing along time (**Figure S4 in Supplementary Appendix 1**). Kaplan-Meier survival curves obtained before and after the time-stratified ATT weighting are presented in **Figure 2**. ATT weighting induced a decrease in one-year survival rate in the conservative group from 59% to 43% (95% CI, 0.421 to 0.441) vs. 27% in the invasive group (95% CI, 0.268 to 0.276, remained unchanged after ATT weighting, as expected). The mortality in the invasive group remained significantly higher after time-dependent IPTW (HR, 1.64; 95% CI, 1.60 to 1.69, $p < 0.001$). Life expectancy limited to one year was 117.5 days in the invasive group versus 185.2 days in the conservative group, resulting in a significant loss of 67.7 days (RMST, 95% CI, 65.7 to 69.8).

In the sensitivity analysis, neither the use of ATT weights truncated at the 5th and 95th percentiles nor the use of a different time-stratification pattern changed substantially the HR associated with invasive procedures. Finally, the combination of weighting and further adjustment on baseline covariates (year, age, sex, coexisting conditions, admission source, severity, and academic status) produced a similar hazard ratio (HR, 1.67; 95% CI, 1.63 to 1.73, $p < 0.001$) (**Supplementary Appendix 1**).

DISCUSSION

Several studies support conservative management over invasive approaches,[18,21,22] and there is concern that invasive procedures may worsen the prognosis of older ICU patients.[23,24] Our large nationwide study was designed to describe the association between invasive care and mortality in real-world clinical practice. Our findings suggest that invasive procedures are a negative determinant, but as an observational study, it cannot be concluded as evidence of harm or non-inferiority between the two groups.

However, the high mortality rate in the invasive group is *per se* our main finding. With a one-year survival rate of 27%, it seems reasonable that a large portion of elderly patients may not be best served by invasive care. This calls into question the upward trend of time-limited trials that could lead to ethical misunderstanding, especially as the survival curves separated early on with a rapid decrease in the invasive group. The high proportion of early deaths in the invasive group most likely reflects the natural progression of an irreversible disease rather than complications from the procedure. This interpretation is supported by the strong culture of safety and patient-family engagement in ICU care, which prioritises harm prevention and appropriate treatment escalation.[25]

The need for invasive care is not merely a treatment choice but also a marker of increased severity. Thus, the poor prognosis associated with invasive care is expected and reflects underlying disease severity rather than the direct impact of invasiveness itself. However, if invasiveness reflects increased severity, then a strict dichotomy between invasive and non-invasive approaches may seem overly simplistic, given that the relationship between the degree of invasiveness and prognosis is likely more gradual. This is supported by the sigmoidal relationship between SAPS II and mortality,[26] resembling a dose-response effect. Nevertheless, we deliberately adopted this classification to avoid borderline situations and to describe the two extremes of the therapeutic spectrum in intensive care.

Admittedly, the non-invasive group likely comprises two distinct populations: patients who are not severe enough to require invasive intervention and those who are too critically ill to benefit from it. However, when considered as a whole, the non-invasive group remains fundamentally distinct from the invasive cohort, where a paradigm shift in care is always required. The two populations we studied differ not in the degree of care received but in the nature of care itself. This distinction is crucial, as the decision between invasive and non-invasive management is never incidental[27]; it is always an active choice that carries significant implications for the patient, their family, and the

medical team. For this reason, we did not include different modalities of oxygenation, such as high-flow nasal insufflation or non-invasive ventilation (NIV), in our analysis.

Furthermore, we aimed for the invasive group to reflect the maximal therapeutic investment—at least at the moment of procedure initiation. In this regard, NIV is a treatment that has been shown to improve survival and, as such, is not purely a palliative intervention. However, its role in alleviating respiratory discomfort is increasingly well-documented. NIV has been found to be more effective than oxygen in reducing dyspnoea and decreasing the need for morphine in palliative care patients.[28] This modality is used both to enhance comfort at the end of life[29] and for patients who have declined tracheal intubation.[30] More broadly, it is now integrated into an approach that seeks to improve palliative care in the ICU.[31]

Finally, this distinction between invasive and non-invasive care also implies the notion of immediacy, which is why we excluded chronic conditions requiring invasive procedures. Both NIV and renal replacement therapy (RRT) are commonly used in chronic settings—NIV for chronic respiratory failure (e.g., amyotrophic lateral sclerosis) and RRT for end-stage renal disease. The coding system does not allow for differentiation between acute and chronic indications. Including these cases would have introduced additional confounding factors, whereas our focus was on invasive procedures initiated for acute conditions. Nevertheless, our findings suggest that renal support worsens prognosis regardless of the treatment group, as among the 8,761 patients who underwent renal replacement therapy, 74% died within one year.

The strength of this study is the size of the cohort with few missing data and the national-level database needed to overcome sampling biases[32] that often limit epidemiological studies of the critically ill elderly. With 107,014 patients under observation, we had the statistical power to robustly assess this issue in the target population of medical ICU patients adjusted for known prognostic

factors specified a priori. The comprehensive multicentre design enhances the generalizability of our findings, particularly important given that older patients are frequently excluded from clinical trials[33] but are commonly treated in the ICU. Our study further provides valuable information on the epidemiology of circulatory and respiratory failures in older patients.

The main limitation of our study is the risk of confounding inherent to any observational study, which the propensity score cannot entirely eliminate. As a summary of measured covariates, the propensity score cannot account for unmeasured confounding.[34] In contrast to randomized controlled trials, where randomization is expected to balance both measured and unmeasured covariates across treatment arms, observational studies remain subject to residual confounding.[35] Nonetheless, best practices for the use of propensity score methods with survival or time-to-event[36] outcomes using inverse probability of treatment weighting (IPTW) can help mitigate the effects of confounding in observational studies.[37,38]

Residual confounding may result from the lack of detailed clinical or contextual data involved in the decision to initiate an invasive procedure. These parameters not only influence the decision itself but also impact patient outcomes. The initiation of vasopressor therapy relies on critical information such as arterial pressure, heart rate, and urinary output, while the decision to proceed with invasive mechanical ventilation depends on the patient's level of consciousness, signs of respiratory failure, and oxygen saturation. Comparing patients without this information is challenging. Nevertheless, although our methods do not directly incorporate these physiological parameters individually, they each contribute to the SAPS II score, which serves as the primary severity adjustment factor in our propensity score model. Notably, the density plots indicate that the SAPS-II distribution is not only the strongest determinant of risk in our model, but also closely aligned between invasive and conservative groups after weighting **(Figure S3 in Supplementary Appendix 1)**. In addition, the reason for admission integrates some clinical data.

We acknowledge that clinical parameters influencing invasive procedures are strong predictors of mortality, regardless of the level of invasiveness. Moreover, the need for invasive care serves as a marker of disease severity rather than a direct determinant of prognosis. In our study, the two populations inherently differ in acute severity, which is a key driver of treatment decisions. However, our aim was not to assess the appropriateness of invasive procedures but rather to describe patient outcomes based on treatment intensity, once a treatment pathway has been adopted in real-world practice.

The predominant contribution of SAPS II to our propensity score substantially mitigates the risk of confounding, although it cannot be broken down into its circulatory and ventilatory components, which would have allowed for a more refined adjustment. Nevertheless, SAPS II integrates various parameters that are associated with both prognosis and the decision to initiate an invasive procedure. This duality reflects the inherent overlap between prognosis and therapeutic decision-making in intensive care, where addressing clinical imbalance is expected to neutralise risk.

For instance, in haemodynamics, the 65 mmHg mean arterial pressure threshold was originally established based on retrospective cohort studies[39,40] that demonstrated a strong association between time spent below this threshold and mortality in patients with septic shock. However, vasopressors have since been shown to exert pleiotropic effects,[41] making their overall impact more difficult to predict, or even potentially leading to increased mortality in older patients.[42]

Thus, the traditional perspective in which invasive procedures were assumed to have an inherently positive—or at worst, neutral—impact by counteracting the excess risk associated with a high severity score has evolved. It is now recognised that their effect is far less predictable and, particularly in older patients, unlikely to be neutral.[43]

Our aim was to describe the trajectories of two distinct ICU populations rather than to compare treatment efficacy. Thanks to the inclusion of all treated patients nationwide over a six-year period, any biases in our data are more likely to reflect overall clinical practice rather than individual decisions regarding the appropriateness of invasive or conservative treatment. This is arguably the main advantage of real-world evidence over randomised trials in informing public health decision-making.[44]

Other limitations of our study include potential biases due to coding errors. Moreover, our study did not include the functional status nor quality of life among survivors, which are more important than survival for many older persons.[45–47] The study also lacks consideration for preexisting frailty, despite its recognized importance as a determinant of mortality.[48–50] However, while elderly patients with a higher functional baseline are more likely to survive, their chances of returning to their prior level are reduced compared to those with a lower functional baseline.[51,52] In addition, whoever with a good functional status is resuscitated until it becomes poor is doomed to die with a poor functional status. The absence of consideration for triage process, treatment appropriateness, or therapeutic limitations may introduce selection bias but reflects the real-world shared decision-making process among physicians, patients, and families. Current studies suggest that the risk of overutilization of invasive procedures outweighs the risk of underutilization[22,24,53–55]

The "*Principles of Biomedical Ethics*" by Beauchamp and Childress, developed in 1979 the four principles of medical care: autonomy, non-maleficence, beneficence, and justice. Individuals have a significant preference for non-maleficence over the other principles, but it does not appear to be directly utilized in the decision-making process.[56] Advance care planning is essential to support clinicians in targeting appropriate invasive, rehabilitative, or palliative strategies which are not exclusive. As stated in a recent review: all critically ill patients, by definition, have serious illness and

thus have palliative care needs.[57] The retrospective meaning of "end-of-life care" seems problematic unless considering the oldest patients are living the last part of their lives. Oldest patients, similar to paediatric patients, have distinct healthcare trajectories and goals supported by physiological evidence for geriatric specificities.

To clarify, our study does not suggest that elderly patients should be denied ICU admission. On the contrary, it highlights the potential benefits of an intensive integrative approach in the ICU rather than a purely technical approach that may only prolong the dying process.[58] The conservative group exhibits a low mortality rate, including patients who were refused invasive treatments due to futility, and it is unlikely to be further reduced with a more invasive approach. Similarly, the high mortality rate observed in the invasive group is unlikely to be exacerbated by a less aggressive strategy.

Our findings have strong ethical implications. Despite being highly selected for favourable outcomes in real-world practice, patients who received invasive procedures had a low survival rate. The incentive care policy for a standard of care regardless of age is questionable in the light of medical appropriateness[22,24,53–55] and patients' wishes.[24–26] While age should not be the sole criterion for ICU triage, the combination of age and the need for an invasive procedure must be considered attentively when deciding on treatment options. Growing evidence suggests a gap between patient preferences and the actual care provided[59] and that focusing resources on patient preferences is possible.[60] Age remains a potent trigger for clinicians to ensure that patients and families are well-informed about the benefits, risks, and harms associated with invasive care.[61]

CONCLUSIONS

In conclusion, in our nationwide study, an invasive approach was associated with a lower one-year survival rate among elderly patients who were admitted to the ICU for medical reasons compared to a conservative approach. Early discussion, including the requirement for an invasive procedure, may

reduce the incidence of avoidable aggressive end-of-life care and improve goal-concordant care achievement.

CONTRIBUTORS

This analysis is an investigator-initiated study led by Clement Leclaire, he supervised the analyses, drafted the manuscript and is the guarantor. All co-authors contributed to the study design and made substantial contribution. AG and CL conceptualised the study and prepared the original study protocol, which was subsequently reviewed by MDS and PA. CL, AG and PA developed the statistical methods. CL and PA had full access to the data, and take responsibility for the integrity of the data and accuracy of the analysis. All authors contributed to data interpretation, critically revised the drafted manuscript and approved the final submitted version. The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have

an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

ETHICS APPROVAL

The study was submitted to and approved by the independent national data protection authority (**CNIL Registration: 920181**). All data were deidentified for research purposes, and French law waives the need for informed consent. An independent institutional review board approved the study protocol (**IRB Registration: #00011928**).

TRANSPARENCY

The manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as originally planned have been explained.

FUNDING

This study was supported by Assistance Publique–Hôpitaux de Paris through an agreement between the CNAM (Caisse Nationale d'Assurance Maladie) and HAD-APHP (signed on October 19, 2020) for the OCTO-Reverse project (962976). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

DATA AVAILABILITY STATEMENT

The data used in this study are derived from the French National Health Data System, which is managed by the French National Health Insurance Fund. Access to these data is subject to regulatory approval and can be requested through the official data access platform under authorization number TPS

962976. Further details on data access procedures can be obtained by contacting snds.cnam@assurance-maladie.fr

REFERENCES

1. Vallet H, Schwarz GL, Flaatten H, de Lange DW, Guidet B, Dechartres A. Mortality of Older Patients Admitted to an ICU: A Systematic Review. Crit Care Med. 2021 Feb 1;49(2):324–34.
2. Baldwin MR. Measuring and predicting long-term outcomes in older survivors of critical illness. Minerva Anestesiol. 2015 Jun;81(6):650–61.
3. Boumendil A, Latouche A, Guidet B, ICE-CUB Study Group. On the benefit of intensive care for very old patients. Arch Intern Med. 2011 Jun 27;171(12):1116–7.
4. Biddison LD, Berkowitz KA, Courtney B, De Jong CMJ, Devereaux AV, Kissoon N, et al. Ethical Considerations: Care of the Critically Ill and Injured During Pandemics and Disasters: CHEST Consensus Statement. Chest. 2014 Oct 1;146(4, Supplement):e145S-e155S.
5. Soliman IW, Cremer OL, de Lange DW, Slooter AJC, van Delden JHJM, van Dijk D, et al. The ability of intensive care unit physicians to estimate long-term prognosis in survivors of critical illness. J Crit Care. 2018 Feb;43:148–55.
6. Vink EE, Azoulay E, Caplan A, Kompanje EJO, Bakker J. Time-limited trial of intensive care treatment: an overview of current literature. Intensive Care Med. 2018 Sep 1;44(9):1369–77.
7. Guidet B, Vallet H, Boddaert J, de Lange DW, Morandi A, Leblanc G, et al. Caring for the critically ill patients over 80: a narrative review. Ann Intensive Care. 2018 Nov 26;8(1):114.
8. Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. JAMA Intern Med. 2015 Apr;175(4):523–9.
9. Flaatten H, de Lange DW, Artigas A, Bin D, Moreno R, Christensen S, et al. The status of intensive care medicine research and a future agenda for very old patients in the ICU. Intensive Care Med. 2017 Sep;43(9):1319–28.
10. Seethala RR, Blackney K, Hou P, Kaafarani HMA, Yeh DD, Aisiku I, et al. The Association of Age With Short-Term and Long-Term Mortality in Adults Admitted to the Intensive Care Unit. J Intensive Care Med. 2017 Oct;32(9):554–8.
11. Nathanson BH, Higgins TL, Brennan MJ, Kramer AA, Stark M, Teres D. Do elderly patients fare well in the ICU? Chest. 2011 Apr;139(4):825–31.
12. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. JAMA. 2010 Mar 3;303(9):849–56.
13. Jubran A, Grant BJB, Duffner LA, Collins EG, Lanuza DM, Hoffman LA, et al. Long-Term Outcome after Prolonged Mechanical Ventilation. A Long-Term Acute-Care Hospital Study. Am J Respir Crit Care Med. 2019 Jun 15;199(12):1508–16.

14. Biston P, Aldecoa C, Devriendt J, Madl C, Chochrad D, Vincent JL, et al. Outcome of elderly patients with circulatory failure. Intensive Care Med. 2014 Jan;40(1):50–6.

15. Fassier T, Duclos A, Abbas-Chorfa F, Couray-Targe S, West TE, Argaud L, et al. Elderly patients hospitalized in the ICU in France: a population-based study using secondary data from the national hospital discharge database. J Eval Clin Pract. 2016 Jun;22(3):378–86.

16. Atramont A, Lindecker-Cournil V, Rudant J, Tajahmady A, Drewniak N, Fouard A, et al. Association of Age With Short-term and Long-term Mortality Among Patients Discharged From Intensive Care Units in France. JAMA Netw Open. 2019 May 3;2(5):e193215.

17. Laporte L, Hermetet C, Jouan Y, Gaborit C, Rouve E, Shea KM, et al. Ten-year trends in intensive care admissions for respiratory infections in the elderly. Ann Intensive Care. 2018 Aug 15;8(1):84.

18. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016 Jul 14;375(2):122–33.

19. Hernán MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. Stat Med. 2002 Jun 30;21(12):1689–709.

20. Austin PC, Thomas N, Rubin DB. Covariate-adjusted survival analyses in propensity-score matched samples: Imputing potential time-to-event outcomes. Stat Methods Med Res. 2020 Mar;29(3):728–51.

21. Auriemma CL, Van den Berghe G, Halpern SD. Less is more in critical care is supported by evidence-based medicine. Intensive Care Med. 2019 Dec 1;45(12):1806–9.

22. Chang DW, Shapiro MF. Association Between Intensive Care Unit Utilization During Hospitalization and Costs, Use of Invasive Procedures, and Mortality. JAMA Intern Med. 2016 Oct 1;176(10):1492–9.

23. Guidet B, Leblanc G, Simon T, Woimant M, Quenot JP, Ganansia O, et al. Effect of Systematic Intensive Care Unit Triage on Long-term Mortality Among Critically Ill Elderly Patients in France: A Randomized Clinical Trial. JAMA. 2017 17;318(15):1450–9.

24. Sjoding MW, Prescott HC, Wunsch H, Iwashyna TJ, Cooke CR. Hospitals with the highest intensive care utilization provide lower quality pneumonia care to the elderly. Crit Care Med. 2015 Jun;43(6):1178–86.

25. Thornton KC, Schwarz JJ, Gross AK, Anderson WG, Liu KD, Romig MC, et al. Preventing Harm in the ICU-Building a Culture of Safety and Engaging Patients and Families. Crit Care Med. 2017 Sep;45(9):1531–7.

26. Aegerter P, Boumendil A, Retbi A, Minvielle E, Dervaux B, Guidet B. SAPS II revisited. Intensive Care Med. 2005 Mar;31(3):416–23.

27. Burns KEA, Cook DJ, Xu K, Dodek P, Villar J, Jones A, et al. Differences in directives to limit treatment and discontinue mechanical ventilation between elderly and very elderly patients: a substudy of a multinational observational study. Intensive Care Medicine [Internet]. 2023 [cited

2025 Mar 18];49(10). Available from: https://link.springer.com/epdf/10.1007/s00134-023-07188-4

28. Nava S, Ferrer M, Esquinas A, Scala R, Groff P, Cosentini R, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. Lancet Oncol. 2013 Mar;14(3):219–27.

29. Azoulay E, Kouatchet A, Jaber S, Meziani F, Papazian L, Brochard L, et al. Non-invasive ventilation for end-of-life oncology patients. Lancet Oncol. 2013 May;14(6):e200-201.

30. Azoulay E, Kouatchet A, Jaber S, Lambert J, Meziani F, Schmidt M, et al. Noninvasive mechanical ventilation in patients having declined tracheal intubation. Intensive Care Med. 2013 Feb;39(2):292–301.

31. Puntillo K, Nelson JE, Weissman D, Curtis R, Weiss S, Frontera J, et al. Palliative care in the ICU: relief of pain, dyspnea, and thirst--a report from the IPAL-ICU Advisory Board. Intensive Care Med. 2014 Feb;40(2):235–48.

32. Hua M, Gershengorn HB, Wunsch H. Assessing delivery of mechanical ventilation: risks and benefits of large databases. Intensive Care Med. 2020 Aug 26;1–4.

33. Ivie RMJ, Vail EA, Wunsch H, Goldklang MP, Fowler R, Moitra VK. Patient Eligibility for Randomized Controlled Trials in Critical Care Medicine: An International Two-Center Observational Study*. Critical Care Medicine. 2017 Feb;45(2):216.

34. Yang JY, Webster-Clark M, Lund JL, Sandler RS, Dellon ES, Stürmer T. Propensity score methods to control for confounding in observational cohort studies: a statistical primer and application to endoscopy research. Gastrointest Endosc. 2019 Sep;90(3):360–9.

35. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009 Nov 10;28(25):3083–107.

36. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014 Mar 30;33(7):1242–58.

37. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011 May;46(3):399–424.

38. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015 Dec 10;34(28):3661–79.

39. Dünser MW, Takala J, Ulmer H, Mayr VD, Luckner G, Jochberger S, et al. Arterial blood pressure during early sepsis and outcome. Intensive Care Med. 2009 Jul;35(7):1225–33.

40. Maheshwari K, Nathanson BH, Munson SH, Khangulov V, Stevens M, Badani H, et al. The relationship between ICU hypotension and in-hospital mortality and morbidity in septic patients. Intensive Care Med. 2018 Jun;44(6):857–67.

41. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. Intensive Care Med. 2016 Sep;42(9):1387–97.

42. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. JAMA. 2017 Oct 10;318(14):1346–57.

43. Lamontagne F, Richards-Belle A, Thomas K, Harrison DA, Sadique MZ, Grieve RD, et al. Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension: A Randomized Clinical Trial. JAMA. 2020 Mar 10;323(10):938–49.

44. Sheldrick RC. Randomized Trials vs Real-world Evidence: How Can Both Inform Decision-making? JAMA. 2023 Apr 25;329(16):1352–3.

45. Philippart F, Vesin A, Bruel C, Kpodji A, Durand-Gasselin B, Garçon P, et al. The ETHICA study (part I): elderly's thoughts about intensive care unit admission for life-sustaining treatments. Intensive Care Med. 2013 Sep;39(9):1565–73.

46. Behforouz HL, Drain PK, Rhatigan JJ. Rethinking the Social History. New England Journal of Medicine. 2014 Oct 2;371(14):1277–9.

47. Le Guen J, Boumendil A, Guidet B, Corvol A, Saint-Jean O, Somme D. Are elderly patients' opinions sought before admission to an intensive care unit? Results of the ICE-CUB study. Age Ageing. 2016 Mar;45(2):303–9.

48. Flaatten H, De Lange DW, Morandi A, Andersen FH, Artigas A, Bertolini G, et al. The impact of frailty on ICU and 30-day mortality and the level of care in very elderly patients (≥ 80 years). Intensive Care Med. 2017 Dec;43(12):1820–8.

49. Guidet B, de Lange DW, Boumendil A, Leaver S, Watson X, Boulanger C, et al. The contribution of frailty, cognition, activity of daily life and comorbidities on outcome in acutely admitted patients over 80 years in European ICUs: the VIP2 study. Intensive Care Med. 2019 Nov 29;

50. Muscedere J, Waters B, Varambally A, Bagshaw SM, Boyd JG, Maslove D, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med. 2017 Aug;43(8):1105–22.

51. Heyland DK, Garland A, Bagshaw SM, Cook D, Rockwood K, Stelfox HT, et al. Recovery after critical illness in patients aged 80 years or older: a multi-center prospective observational cohort study. Intensive Care Med. 2015 Nov;41(11):1911–20.

52. Griffiths J, Hatch RA, Bishop J, Morgan K, Jenkinson C, Cuthbertson BH, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care. 2013 May 28;17(3):R100.

53. Teno JM, Gozalo P, Khandelwal N, Curtis JR, Meltzer D, Engelberg R, et al. Association of Increasing Use of Mechanical Ventilation Among Nursing Home Residents With Advanced Dementia and Intensive Care Unit Beds. JAMA Intern Med. 2016 Dec 1;176(12):1809–16.

54. Sullivan DR, Kim H, Gozalo PL, Bunker J, Teno JM. Trends in Noninvasive and Invasive Mechanical Ventilation Among Medicare Beneficiaries at the End of Life. JAMA Intern Med. 2020 Oct 19;

55. Guidet B, Flaatten H, Boumendil A, Morandi A, Andersen FH, Artigas A, et al. Withholding or withdrawing of life-sustaining therapy in older adults (≥ 80 years) admitted to the intensive care unit. Intensive Care Med. 2018;44(7):1027–38.

56. Page K. The four principles: Can they be measured and do they predict ethical decision making? BMC Med Ethics. 2012 May 20;13:10.

57. Aslakson RA, Cox CE, Baggs JG, Curtis JR. Palliative and End-of-Life Care: Prioritizing Compassion Within the ICU and Beyond. Critical Care Medicine. 2021 Oct;49(10):1626–37.

58. Cox CE, Curtis JR. Using Technology to Create a More Humanistic Approach to Integrating Palliative Care into the Intensive Care Unit. Am J Respir Crit Care Med. 2016 Feb 1;193(3):242–50.

59. Heyland DK, Dodek P, Mehta S, Cook D, Garland A, Stelfox HT, et al. Admission of the very elderly to the intensive care unit: family members' perspectives on clinical decision-making from a multicenter cohort study. Palliat Med. 2015 Apr;29(4):324–35.

60. Deniau N, Shojaei T, Georges A, Danis J, Czapiuk G, Mercier S, et al. Home emergency response team for the seriously ill palliative care patient: feasibility and effectiveness. BMJ Support Palliat Care. 2023 Oct 16;spcare-2023-004385.

61. Leblanc G, Boumendil A, Guidet B. Ten things to know about critically ill elderly patients. Intensive Care Med. 2017 Feb;43(2):217–9.

Table 1. Patient characteristics*

	All Patients (N = 107 014)	Invasive Group (N = 51 680)	Conservative Group (N = 55 334)	P Value
Percentage of patients	100	48	52	
Mean age – Yr	84.6 ± 3.6	84.3 ± 3.4	84.9 ± 3.7	< 0.001
Male sex – no (%)	53 457 (50)	26 785 (52)	26 672 (48)	< 0.001

Year of enrolment – no (%)				< 0.001
2013	17 138 (16)	7 756 (15)	9 382 (17)	
2014	17 484 (16)	8 013 (16)	9 471 (17)	
2015	18 286 (17)	8 612 (17)	9 674 (18)	
2016	18 312 (17)	9 143 (18)	9 169 (17)	
2017	18 284 (17)	9 236 (18)	9 048 (16)	
2018	17 510 (16)	8 920 (17)	8 590 (16)	
Admission source – no (%)				< 0.001
Home	31 703 (30)	15 079 (29)	16 624 (30)	
Emergency department	63 032 (59)	30 446 (59)	32 586 (59)	
Other skilled facility	12 279 (11)	6 155 (12)	6 124 (11)	
Hospital status – no (%)				< 0.001
Private	17 411 (16)	5 226 (10)	12 185 (22)	
Public academic	28 394 (27)	15 024 (29)	13 370 (24)	
Public non-academic	61 209 (57)	31 430 (61)	29 779 (54)	
Geriatric team in the hospital – no (%)	78 973 (74)	41 717 (81)	37 256 (67)	< 0.001
Palliative care team in the hospital – no (%)	61 089 (57)	33 089 (64)	28 000 (51)	< 0.001
Coexisting conditions – no (%)				< 0.001
Cardiac Disease	39 659 (37)	18 384 (36)	21 275 (39)	
Respiratory disease	31 807 (30)	14 046 (27)	17 761 (32)	
Renal disease	28 344 (27)	12 937 (25)	15 407 (28)	
Neurologic disease	12 062 (11)	6 305 (12)	5 757 (10)	
Cognitive impairment	10 651 (10)	4 996 (10)	5 655 (10)	
Cirrhosis	3 622 (3)	1 936 (4)	1 686 (3)	
Diabetes	16 191 (15)	7 723 (15)	8 468 (15)	
Cancer	19 162 (18)	9 083 (18)	10 079 (18)	
Charlson comorbidity index (CCI)				< 0.001
Median (Interquartile range)	2 (1 – 4)	2 (1 – 4)	2 (1 – 4)	

CCI = 0	23 972 (22%)	12 698 (25%)	11 274 (20%)	
Immunodeficiency – no (%)	20 753 (19)	9 884 (19)	10 869 (20)	< 0.001
Median SAPS II – (Interquartile range)	45 (34 – 63)	59 (45 – 76)	37 (30 – 46)	< 0.001
Diagnosis category – no (%)				< 0.001
Circulatory	40 189 (38)	20 773 (40)	19 416 (35)	
Respiratory	29 926 (28)	13 682 (27)	16 244 (29)	
Neuro-metabolic	36 899 (35)	17 225 (33)	19 674 (36)	
Outcomes†				< 0.001
One-year mortality – no (%)	58 955 (55)	36 019 (70)	22 936 (41)	
ICU mortality – no (%)	32 160 (30)	26 152 (51)	6 008 (11)	
In-hospital mortality – no (%)	37 354 (35)	28 438 (55)	8 916 (16)	
Median length of stay – days (interquartile range)				< 0.001
In ICU	4 (2 – 8)	5 (2 – 11)	3 (1 – 6)	
In hospital	8 (2 – 16)	7 (1 – 18)	8 (3 – 14)	
ICU readmission within the year – no (%)				< 0.001
In patients from enrolment	23 846 (22)	6 894 (13)	16 952 (31)	
In ICU-survivors	23 846 (32)	6 894 (27)	16 952 (34)	
Hospital discharge for survivors – no (%)				< 0.001
Home	35 312 (51)	9 016 (39)	26 296 (57)	
Other skilled facility	34 348 (49)	14 226 (61)	20 122 (43)	

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.

† Crude unweighted outcomes since ICU admission, without regard for the time-to-event analysis.

Footnote (Table 1): P-values correspond to statistical tests assessing whether there is a significant difference between the two groups. Variation in comorbidity burden and underlying physiological robustness may have influenced the decision to initiate invasive care, contributing to baseline differences between groups.

Table 2. Outcomes in the invasive group (n=51 680)*

	No (%)	Mortality – no (%)			Median length of stay – days (interquartile range)	
		ICU	**Hospital**	**1 Year**	**ICU**	**Hospital**
All vasopressors (± ventilations)	38 427 (74)	20 606 (54)	22 281 (58)	27 694 (72)	5 (2 – 12)	8 (3 – 18)
All ventilations (± vasopressors)	40 495 (78)	22 632 (56)	24 217 (60)	29 331 (72)	5 (2 – 12)	7 (1 – 18)
Vasopressors only	11 185 (22)	3 520 (32)	4 221 (38)	6 688 (60)	5 (2 – 8)	9 (2 – 17)
Ventilations only	13 253 (26)	5 546 (42)	6 157 (47)	8 325 (63)	4 (2 – 9)	9 (3 – 18)
Vasopressors and ventilations	27 242 (53)	17 086 (63)	18 060 (66)	21 006 (77)	6 (2 – 14)	7 (2 – 16)

This table reports the subsets of patients according to the invasive procedures exposure.

* Crude incidence and unweighted outcomes since ICU admission, without regard for the time-to-event analysis.

Percentages may not sum to 100 because of rounding.

FIGURE TITLES/LEGENDS

Figure 1. Flowchart of patients and stays in the study
ICU denotes intensive care unit, and DRG diagnosis-related-groups. DRG errors correspond to stays that could not be assigned to a Diagnosis-Related Group, mainly due to coding inconsistencies or inaccuracies in the classification of hospital stays, such as misclassification of diagnoses, procedures, or administrative coding discrepancies.

Figure 2. Probability of survival from ICU admission to one year, according to conservative or invasive approach, before and after time-dependent propensity score weighting (ATT)

Kaplan-Meier method adapted to time-dependant covariate (with 95% CI). Dashed lines represent time-dependent Kaplan-Meier plot of the probability of survival from ICU admission to one year among the original unweighted population. Solid lines represent time-dependent Kaplan-Meier plot of the probability of survival on IPTW-ATT weighted sample using weights trimmed at the first and 99th percentile. Invasive curve remained unchanged after weighting, as expected. IPTW denotes inverse probability of treatment weighting, ATT denotes average treatment effect in the treated, HR denotes the hazard ratio obtained from the ATT99 weighted Cox model and diff-RMST the difference in (one-year) restricted mean survival time (days).

FIGURE 1. Flowchart of Patients and Stays in the Study

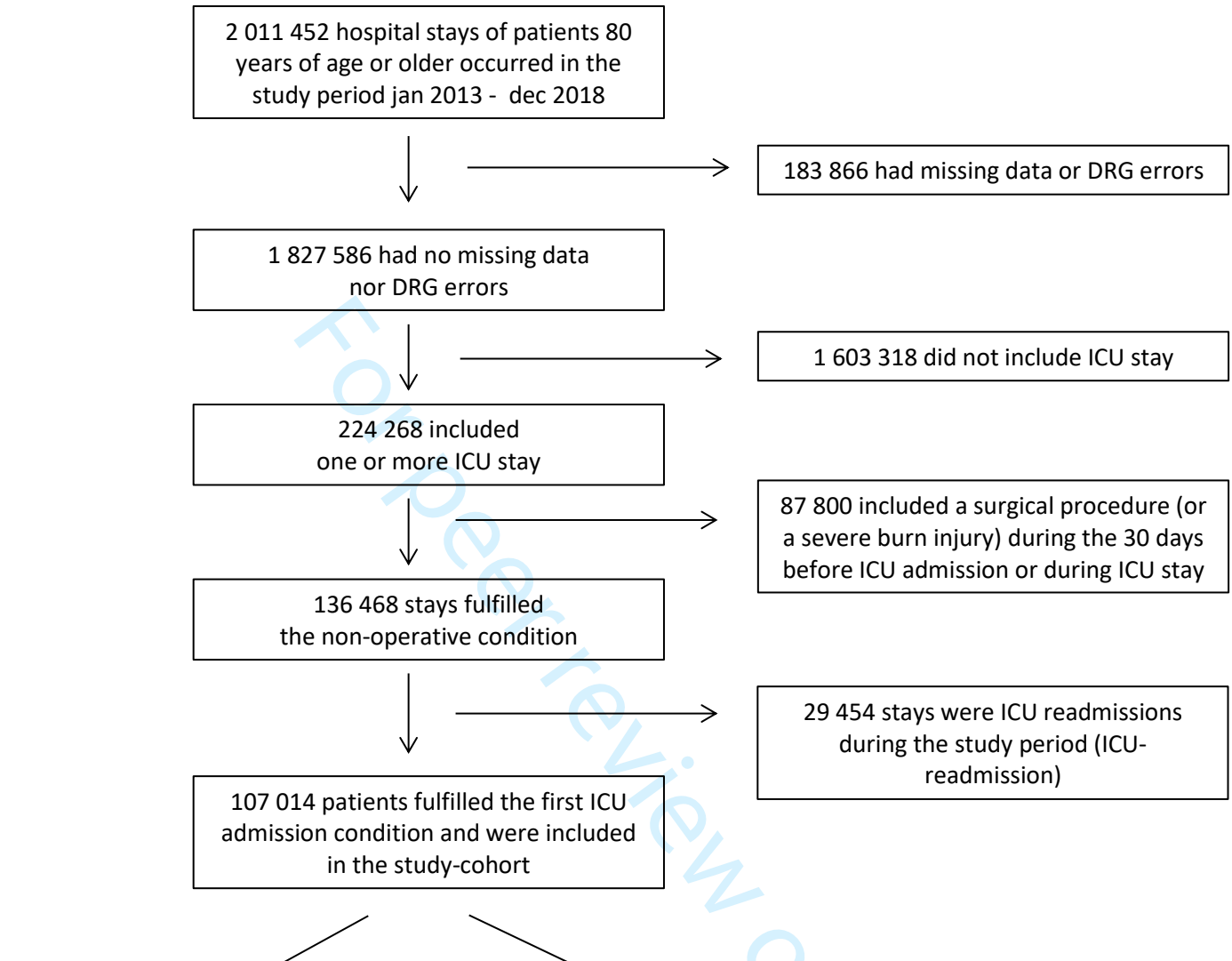
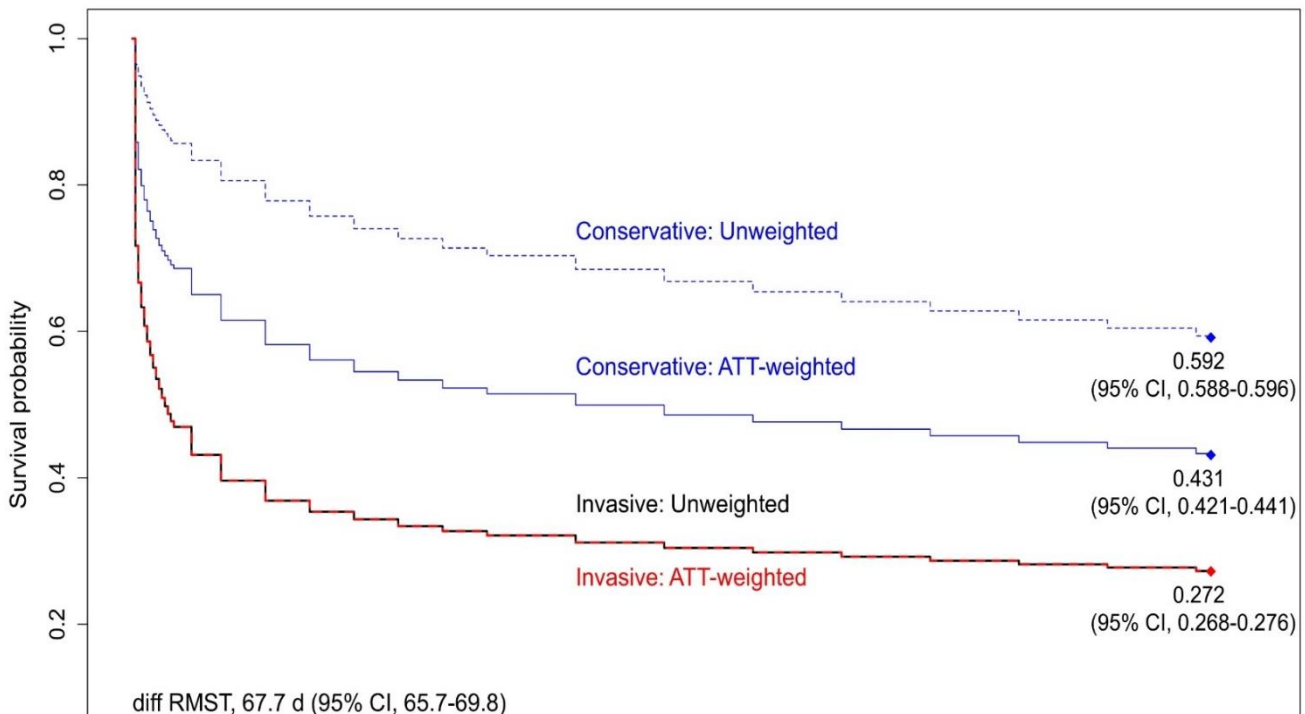


FIGURE 2. Probability of Survival from ICU admission to One Year, according to Conservative or Invasive Approach, Before and After Time-Dependent Propensity Score Weighting (ATT).



SUPPLEMENTARY APPENDIX

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LIST OF INVESTIGATORS AND CONTRIBUTION

This analysis is an investigator-initiated study led by Clement Leclaire, he supervised the analyses, drafted the manuscript and is the guarantor. All co-authors contributed to the study design and made substantial contribution. AG and CL conceptualised the study and prepared the original study protocol, which was subsequently reviewed by MDS and PA. CL, AG and PA developed the statistical methods. CL and PA had full access to the data, and take responsibility for the integrity of the data and accuracy of the analysis. All authors contributed to data interpretation, critically revised the drafted manuscript and approved the final submitted version.

METHODOLOGICAL PLAN

Detailed description of data source - the SNDS Database

We conducted a nationwide retrospective analysis of data prospectively collected in the Système National des Données de Santé (SNDS), the national French health care database that covers around 99% of the population. The SNDS was created to answer epidemiological research questions with specific interests in occupational and social factors, chronic diseases, and aging, including a medico-economic assessment and extended follow-up without attrition bias **[1,2]**.

Using the National hospital discharge database is an established method for elderly patients hospitalized in the ICU in France **[3–5]**. Formal methods have been developed to assess the strengths and limitations of databases **[6,7]**, and population-level data have greatly enhanced our understanding of how mechanical ventilation is utilized and the associated outcomes for patients **[8]**.

The SNDS links the Système National d'Information Interrégimes de l'Assurance Maladie (SNIIRAM), the nationwide health insurance information system, to the national hospital discharge database of Diagnosis-Related Groups (DRG) **[9,10]**, known as Programme de Médicalisation des Systèmes d'Information (PMSI), and to the national death registry, "CépiDC." It includes more than 99% of the French population (66 million people) from birth (or immigration) to death (or emigration), regardless of changes in occupation, retirement, or socioeconomic status. Therefore, the SNDS contains individual pseudonymized information on all medical and paramedical encounters, drug claims, hospital admissions and procedures, as well as the date and cause of death, which are linked to create an individual longitudinal record. This linkage of large-scale national registry populations in France contributes to guiding public decisions **[11,12]**.

The SNDS collects comprehensive medical and administrative data prospectively for all patients in the country and underlies the activity-based hospital payment system. All patients are assigned a unique identification number, allowing for longitudinal follow-up by linking inpatient and outpatient data from each hospitalization in all public or private facilities in France. Hospital data include age, sex, admission and discharge dates and location, vital status at discharge, hospital units visited during the hospitalization, and length of hospitalization. Hospital discharge diagnoses (main, associated, secondary) provide information on the reason for admission (main) and background risk modifiers (e.g., diabetes, renal failure, coronary heart disease) that complicate the care. Associated diagnoses provide information on the reasons for procedures as the main diagnosis. Procedures, both surgical and medical, including life-sustaining treatments, are time-stamped and coded using a national multidimensional classification system called CCAM **[13]**.

These data are utilized for hospital payment **[14]** and government purposes **[12]**, so the quality of coding undergoes regular internal and external audits, both within the hospital information systems and through the national healthcare system's accreditation process **[15]**. Both reliability and completeness are excellent, and a structured assessment of the database has been described elsewhere **[3]**.

Detailed description of statistical analysis

Baseline characteristics of patients were described as frequencies and percentages for categorical variables and as means (with standard deviations, SD) or medians (with interquartile range, IQR) for continuous variables. Bivariate associations were evaluated using the Kruskal-Wallis test for continuous variables and the $\chi 2$ or Fisher exact test for categorical variables, as appropriate. Survival was measured from the date of ICU admission to the date of death or censored at the last follow-up. Since the refreshment of SNDS is periodic across the entire country, the date of the last follow-up was estimated by the 95th percentile of the dates of death.

To limit an immortal time bias, the occurrence of any invasive procedure was considered as a time-dependent covariate. Time precision was at the day level, and the time of death was shifted by 0.1 day to avoid ties with the time of the procedure. Multivariate analysis of survival was performed using a Cox proportional hazards (PH) model, which produced hazard ratios (HR). The handling of ties used the Efron approximation. The PH assumption was verified by scaled Schoenfeld residuals. The Cox model was extended to deal with time-varying effects by adding an interaction term between the given covariate and some transformation of time (step function, continuous power transformation such as first-degree fractional polynomials, or stratification of time). The touchstone for choosing the best approach was the Akaike Information Criterion (AIC) **[16]**. When the effect was time-varying, a unique overall HR was interpreted as a weighted average HR over the event times **[17]**. However, we also summarized this effect with a model-free parameter, the difference in the restricted mean survival time (RMST), which has greater clinical interpretability and represents the loss of life expectancy **[18,19]**.

As patients receiving invasive procedures may differ from conservative ones, a propensity score (PS) was used to minimize the effects of confounding. However, the population at risk changes due to attrition of susceptibles. The conventional method may cause bias with the time-varying exposure because those time-dependent treatment decisions act as time-varying confounders, affecting both the occurrence of the event of interest and the patient's exposure to the treatment of interest **[20]**. Thus, the conventional PS analysis must become time-dependent to address this time-varying effect and be able to estimate measures of effect similar to those obtained in randomized experiments **[21,22]**. To accommodate this, our study made use of the inverse probability of treatment weighting (IPTW) method adapted to the time-dependent context **[23]**.

IPTW usually estimates the average treatment effect (ATE) when the entire sample is moved from control to treated. However, this seemed unrealistic for invasive support in the elderly population. Therefore, IPTW targeted the average treatment effect in the treated (ATT) **[24]**, also called weighting by odds, which denotes the average effect of treatment in those subjects who were ultimately treated, as PS matching does. In such a case, the analysis uses the treated subjects as the reference population to which each group is standardized.

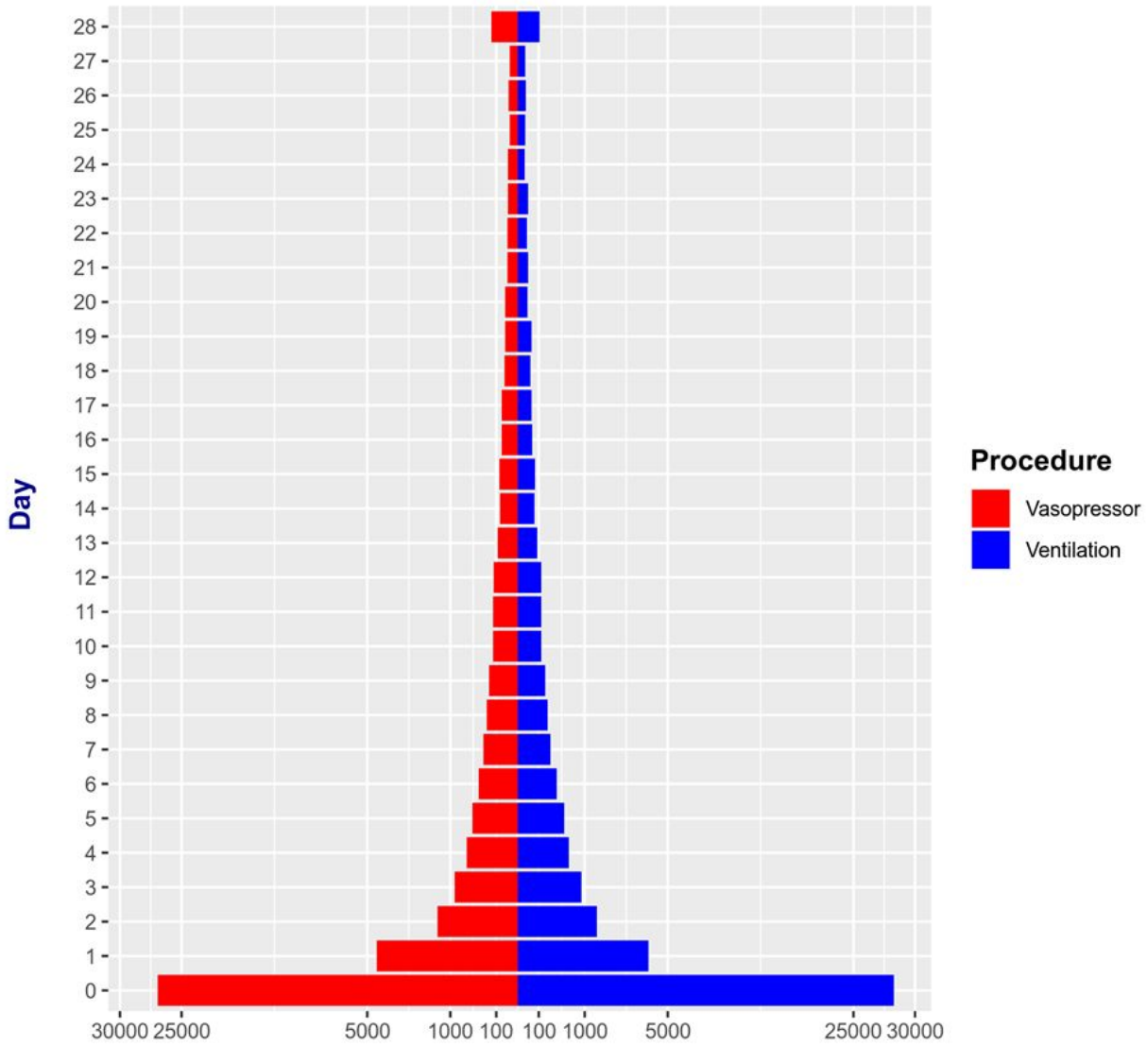
We divided the time span into strata within which a PS was calculated. These strata included each day until day 14, then periods of 14-20, 20-30, every 15 days until 120, and every 30 days until 365 (case base). This time-stratified PS was built using a Cox model that predicted the use of invasive procedures based on variables available at admission. The influence of continuous variables (age and SAPS-II) was modeled by fractional polynomials (FP). Variable balance was assessed by examining the standardized mean differences before and after weighting **[25]**. Weights were trimmed at the first and 99th percentiles. To remove residual confounding, we combined weighting at the sampling stage with regression adjustment at the analysis stage when estimating treatment effects **[26]**. A robust sandwich-type estimator was used to calculate standard errors.

We performed sensitivity analyses to assess the robustness of the overall HR associated with invasive procedures: initially by using ATT weights truncated at the 5th and 95th percentiles, and then by using time strata defined by every day an invasive procedure or death occurred.

All tests were two-sided, and a p-value < 0.05 was considered statistically significant. The analysis was conducted using SAS Enterprise Guide v7.15 (SAS Institute Inc., Cary, NC, USA) provided by the SNDS infrastructure.

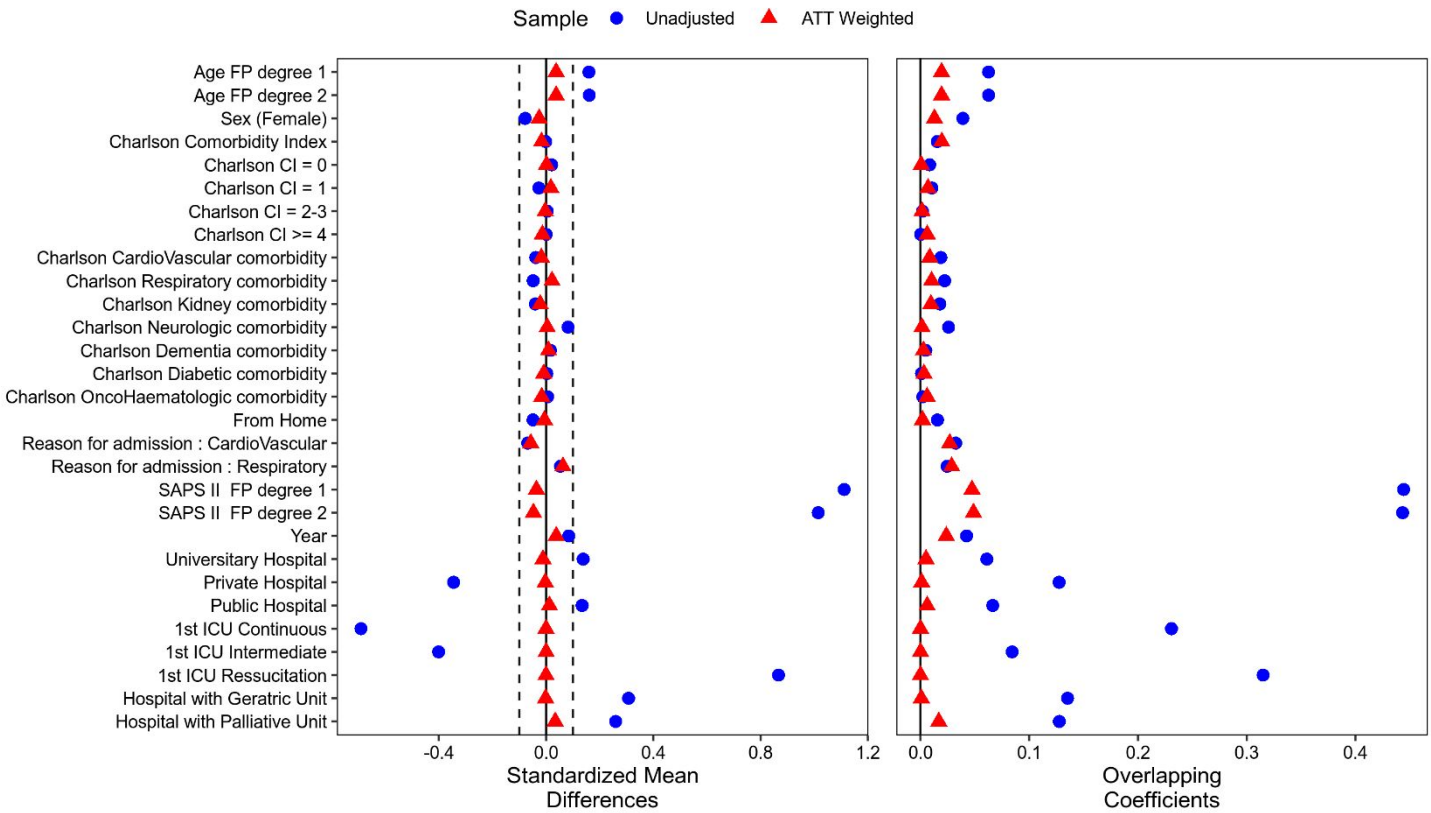
FIGURES

Figure S1: Time until initiation of the invasive procedure since ICU admission (In the invasive group)



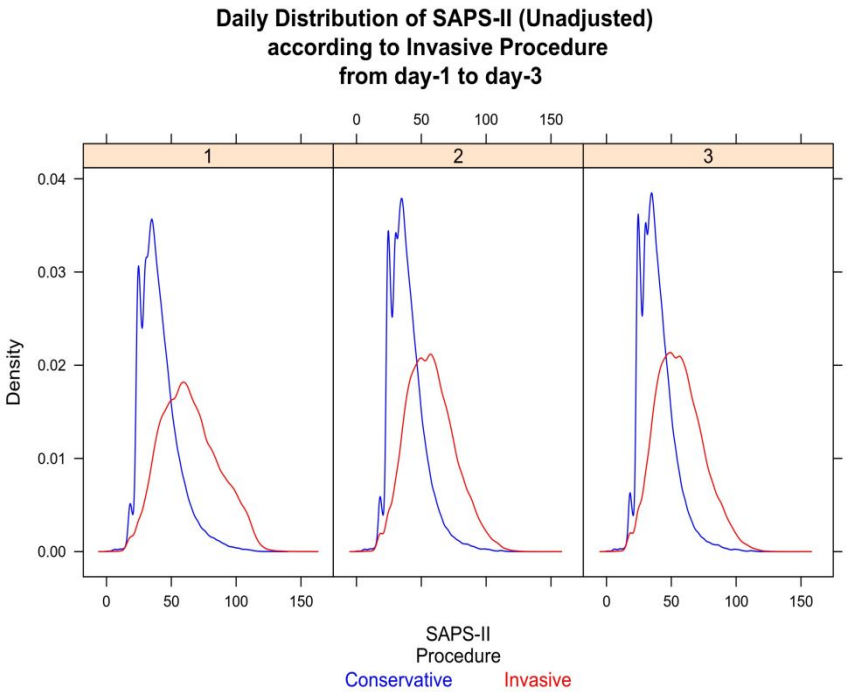
In the invasive group: Number of stays according to the day of initiation of the invasive procedure from ICU-admission (note that the bars at day-28 include stays beyond day-28): Time of initial vasopressor support was the day of ICU-admission for 75% of patients and the following day for 11% more. Time of initial ventilation support was the day of ICU-admission for 77% of patients and the following day for 9% more.

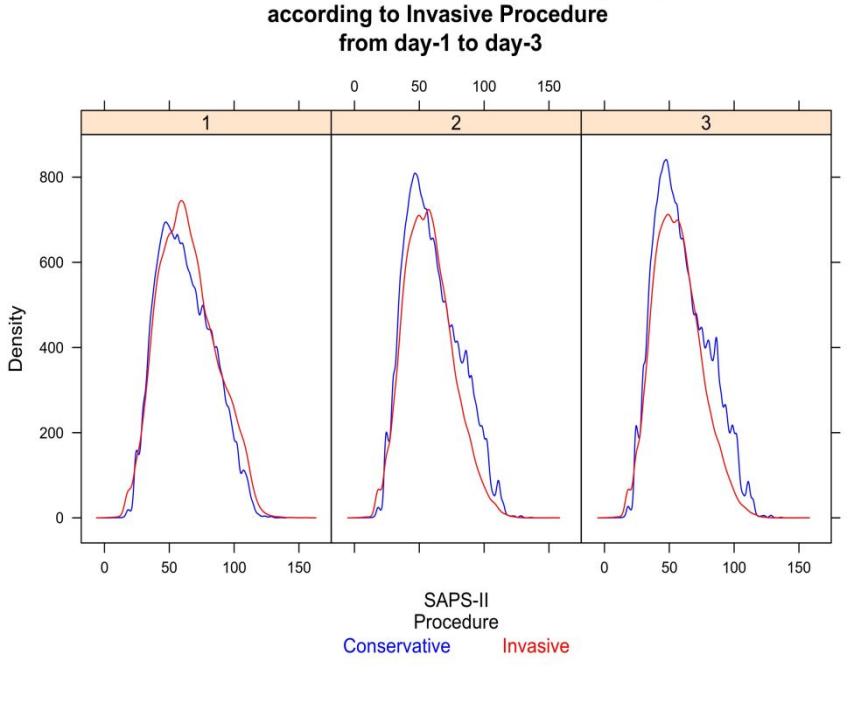
Figure S2: Covariate balance on the whole period



While there were significant differences between invasive and conservative patients in the raw sample, differences in the ATT weighted sample issued from the time-stratified model were minimal, with absolute standardized differences less than 0.1 as shown on the covariate balance aggregating all time strata and on the Love plot.

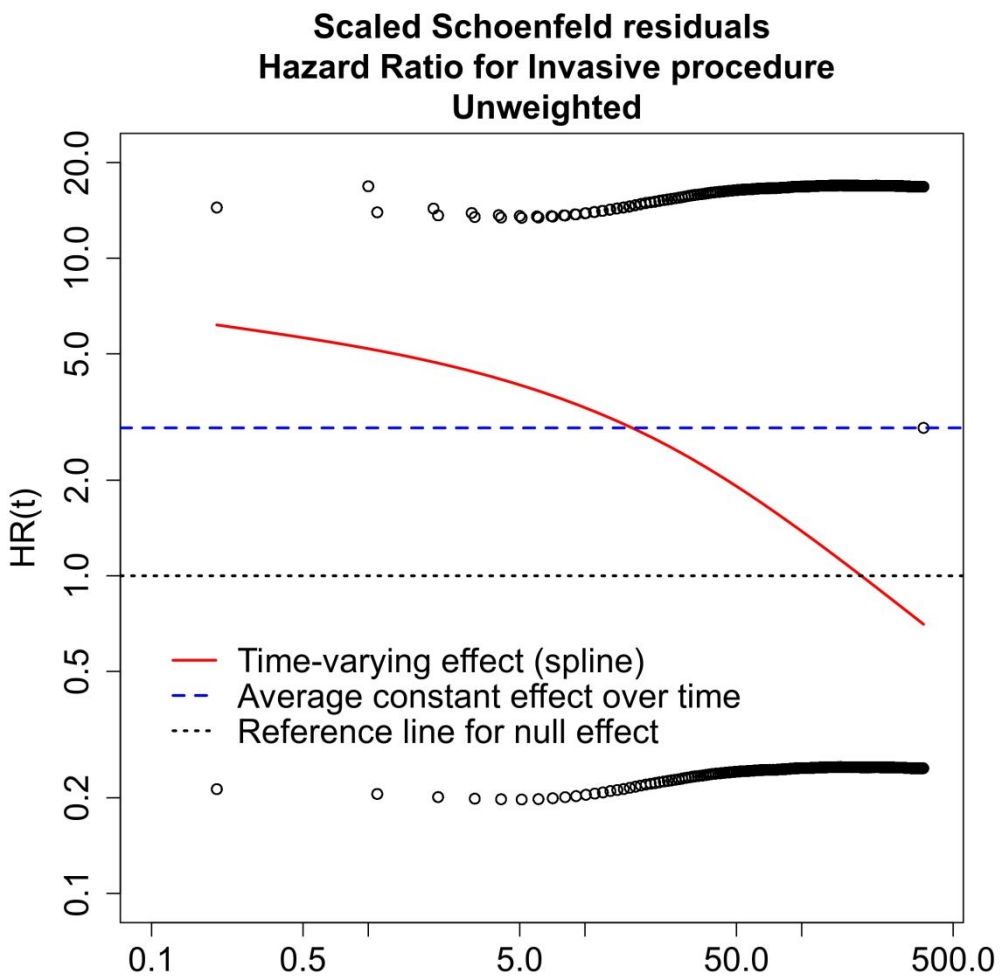
Figure S3: Density plots of daily SAPS-II along the first 3 days, according to invasive/conservative approach, before and after ATT weighting





The density plots shows that the distribution for SAPS-II (the major determinant of risk) along the first 3 days is higher in the invasive group before weighting, and is very much closer after weighting in the two groups.

Figure S4: Time-varying effect of invasive procedure at one year (Shoenfeld residuals / Modelization of time-varying effect)



The test of Schoenfeld residuals for proportional hazards assumption was significant, as the HR was decreasing along time, and was not significantly different from unity after 50 days

TABLES

Table S1: Association of Baseline Factors with death at one year (Cox model)

	Distribution		Univariate			Multivariate		
Variable	**Living at d365**	**Dead at d365**	**HR**	**95 % conf.int**	**P-value**	**HR**	**95 % conf.int**	**P-value**
Age (y)	84.3, 84 (82 - 86)	84.9, 84 (82 - 87)	1.03	[1.02, 1.03]	<0.001	1.04	[1.04, 1.05]	<0.001
Age [80-84]	27932 (58.1)	30949 (52.5)	1					
Age [85-89]	15841 (33)	21043 (35.7)	1.13	[1.11, 1.15]	<0.001	0.99	[0.96, 1.02]	0.510
Age [90+]	4286 (8.9)	6963 (11.8)	1.29	[1.26, 1.32]	<0.001	0.98	[0.92, 1.05]	0.601
Sex female	25524 (53.1)	28033 (47.5)	0.88	[0.87, 0.90]	<0.001	0.90	[0.88, 0.91]	<0.001
From Home	42819 (89.1)	51916 (88.1)	0.96	[0.94, 0.98]	0.001	0.93	[0.91, 0.96]	<0.001
Reason for admission : CardioVascular	16514 (34.4)	23675 (40.2)	1.28	[1.26, 1.30]	<0.001	1.42	[1.39, 1.46]	<0.001
Reason for admission : Respiratory	12617 (26.3)	17309 (29.4)	1.04	[1.02, 1.06]	<0.001	1.20	[1.17, 1.22]	<0.001
SAPS II	41, 38 (30 - 49)	57.9, 54 (40 - 73)	1.04	[1.04, 1.04]	<0.001	1.04	[1.04, 1.04]	<0.001
SAPS II [1-34[	17288 (36)	7913 (13.4)	1			1		
SAPS II [34-45[	14852 (30.9)	12264 (20.8)	1.58	[1.54, 1.62]	<0.001	1.01	[0.98, 1.04]	0.466
SAPS II [45-63[	11250 (23.4)	16677 (28.3)	2.49	[2.43, 2.55]	<0.001	0.95	[0.91, 1.00]	0.029
SAPS II [63-156]	4669 (9.7)	22101 (37.5)	6.18	[6.02, 6.34]	<0.001	0.89	[0.82, 0.95]	0.001
Charlson Comorbidity Index	2.3, 2 (1 - 3)	2.9, 2 (1 - 4)	1.04	[1.04, 1.05]	<0.001	1.05	[1.04, 1.06]	<0.001
Charlson CI = 0	11735 (24.4)	12237 (20.8)	1			1		
Charlson CI = 1	9793 (20.4)	9606 (16.3)	0.89	[0.87, 0.92]	<0.001	0.90	[0.87, 0.93]	<0.001
Charlson CI = 2-3	14821 (30.8)	17918 (30.4)	1.02	[0.99, 1.04]	0.130	0.97	[0.93, 1.00]	0.078
Charlson CI >= 4	11710 (24.4)	19194 (32.6)	1.18	[1.16, 1.21]	<0.001	1.01	[0.95, 1.07]	0.751
Charlson CardioVascular comorbidity	17654 (36.7)	22005 (37.3)	0.97	[0.96, 0.99]	<0.001	0.93	[0.91, 0.96]	<0.001
Charlson Respiratory comorbidity	14013 (29.2)	17794 (30.2)	0.97	[0.95, 0.98]	<0.001	0.98	[0.96, 1.01]	0.138
Charlson Kidney comorbidity	11648 (24.2)	16696 (28.3)	1.08	[1.06, 1.10]	<0.001	0.87	[0.85, 0.90]	<0.001
Charlson Neurologic comorbidity	4758 (9.9)	7304 (12.4)	1.17	[1.14, 1.20]	<0.001	1.00	[0.97, 1.04]	0.871
Charlson Dementia comorbidity	4083 (8.5)	6568 (11.1)	1.18	[1.15, 1.21]	<0.001	1.04	[1.01, 1.07]	0.010
Charlson Diabetic comorbidity	7109 (14.8)	9082 (15.4)	0.99	[0.97, 1.02]	0.578	0.84	[0.81, 0.86]	<0.001
Charlson OncoHaematologic comorbidity	6857 (14.3)	12305 (20.9)	1.27	[1.25, 1.29]	<0.001	0.99	[0.96, 1.03]	0.590
Year 2013	7945 (16.5)	9193 (15.6)	1			1		
Year 2014	7839 (16.3)	9645 (16.4)	1.04	[1.01, 1.07]	0.003	1.03	[1.00, 1.07]	0.029
Year 2015	8328 (17.3)	9958 (16.9)	1.03	[1.00, 1.06]	0.031	1.00	[0.97, 1.03]	0.949
Year 2016	8137 (16.9)	10175 (17.3)	1.06	[1.03, 1.09]	<0.001	1.00	[0.97, 1.04]	0.835

Year 2017	8041 (16.7)	10243 (17.4)	1.08	[1.05, 1.11]	<0.001	1.00	[0.97, 1.03]	0.933
Year 2018	7769 (16.2)	9741 (16.5)	1.07	[1.04, 1.10]	<0.001	0.98	[0.95, 1.01]	0.193
Universitary Hospital	12992 (27)	15402 (26.1)	1			1		
Private Hospital	9179 (19.1)	8232 (14)	0.76	[0.74, 0.78]	<0.001	1.15	[1.10, 1.20]	<0.001
Public Hospital	25888 (53.9)	35321 (59.9)	1.08	[1.06, 1.10]	<0.001	1.09	[1.07, 1.12]	<0.001
1st ICU Continuous monitoring	9084 (18.9)	6007 (10.2)	1			1		
1st ICU Intermediate	3290 (6.8)	1534 (2.6)	0.76	[0.72, 0.80]	<0.001	0.84	[0.79, 0.88]	<0.001
1st ICU Ressucitation	35685 (74.3)	51414 (87.2)	1.95	[1.90, 1.99]	<0.001	1.18	[1.14, 1.21]	<0.001
Hospital with Geriatric Unit	33848 (70.4)	45125 (76.5)	1.31	[1.28, 1.33]	<0.001	1.10	[1.06, 1.13]	<0.001
Hospital with Palliative Unit	25803 (53.7)	35287 (59.9)	1.23	[1.21, 1.25]	<0.001	1.01	[0.98, 1.03]	0.638

This table presents which baseline-factors are associated with death at one year in univariate and multivariate survival analysis. As expected, SAPS II showed the higher association with death.

Table S2: CCAM Codes of invasive procedures

Support	Code	French label	Translation
Ventilation	**GLLD004**	Ventilation mécanique intratrachéale avec pression expiratoire positive [PEP] supérieure à 6 et/ou FiO2 supérieure à 60%, avec technique de décubitus ventral alterné par 24 heures	Intratracheal mechanical ventilation with Positive End Expiratory Pressure [PEEP] greater than 6 and/or FiO2 greater than 60%, with alternating prone position technique per 24 hours
	GLLD008	Ventilation mécanique intratrachéale avec pression expiratoire positive [PEP] supérieure à 6 et/ou FiO2 supérieure à 60%, par 24 heures	Intratracheal mechanical ventilation with Positive End Expiratory Pressure [PEEP] greater than 6 and/or FiO2 greater than 60%, per 24 hours
	GLLD015	Ventilation mécanique intratrachéale avec pression expiratoire positive [PEP] inférieure ou égale à 6 et FiO2 inférieure ou égale à 60%, par 24 heures	Intratracheal mechanical ventilation with Positive End Expiratory Pressure [PEEP] less than or equal to 6 and FiO2 less than or equal to 60%, per 24 hours
Circulation	**EQLF001**	Injection intraveineuse continue de dobutamine ou de dopamine à débit inférieur à 8 microgrammes par kilogramme par minute [µg/kg/min], ou de dopexamine en dehors de la période néonatale, par 24 heures	Continuous intravenous infusion of dobutamine or dopamine at a dose less than 8 micrograms per kilogram per minute [µg/kg/min], or dopexamine outside the neonatal period, per 24 hours
	EQLF003	Injection intraveineuse continue de dobutamine ou de dopamine à débit supérieur à 8 microgrammes par kilogramme par minute [µg/kg/min], d'adrénaline ou de noradrénaline en dehors de la période néonatale, par 24 heures	Continuous intravenous infusion of dobutamine or dopamine at a dose greater than 8 micrograms per kilogram per minute [µg/kg/min], epinephrine or norepinephrine outside the neonatal period, per 24 hours

CCAM = the Classification Commune des Actes Médicaux is the common French Social Security classification of all medical procedures

REFERENCES

1. Scailteux LM, Droitcourt C, Balusson F, et al. French administrative health care database (SNDS): The value of its enrichment. *Therapie* 2019; **74:** 215–223.

2. Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017; **26:** 954–962.

3. Fassier T, Duclos A, Abbas-Chorfa F, et al. Elderly patients hospitalized in the ICU in France: a population-based study using secondary data from the national hospital discharge database. *J Eval Clin Pract* 2016; **22:** 378–386.

4. Laporte L, Hermetet C, Jouan Y, et al. Ten-year trends in intensive care admissions for respiratory infections in the elderly. *Ann Intensive Care* 2018; **8:** 84.

5. Atramont A, Lindecker-Cournil V, Rudant J, et al. Association of Age With Short-term and Long-term Mortality Among Patients Discharged From Intensive Care Units in France. *JAMA Netw Open* 2019; **2:** e193215.

6. Cooke CR, Iwashyna TJ. Using existing data to address important clinical questions in critical care. *Crit Care Med* 2013; **41:** 886–896.

7. Black N, Payne M. Directory of clinical databases: improving and promoting their use. *Qual Saf Health Care* 2003; **12:** 348–352.

8. Hua M, Gershengorn HB, Wunsch H. Assessing delivery of mechanical ventilation: risks and benefits of large databases. *Intensive Care Med* 2020; 1–4.

9. Ettelt S, Nolte E. Funding Intensive Care - Approaches in Systems Using Diagnosis-Related Groups. *Rand Health Q* 2012; **1:** 7.

10. Busse R, Geissler A, Aaviksoo A, et al. Diagnosis related groups in Europe: moving towards transparency, efficiency, and quality in hospitals? *BMJ* 2013; **346:** f3197.

11. Didier R, Gouysse M, Eltchaninoff H, et al. Successful linkage of French large-scale national registry populations to national reimbursement data: Improved data completeness and minimized loss to follow-up. *Arch Cardiovasc Dis* 2020; **113:** 534–541.

12. Tuppin P, Rudant J, Constantinou P, et al. Value of a national administrative database to guide public decisions: From the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique* 2017; **65:** S149–S167.

13. Trombert-Paviot B, Rector A, Baud R, et al. The development of CCAM: the new French coding system of clinical procedures. *Health Inf Manag J Health Inf Manag Assoc Aust* 2003; **31:** 1–11.

14. Bittner MI, Donnelly M, van Zanten AR, et al. How is intensive care reimbursed? A review of eight European countries. *Ann Intensive Care* 2013; **3:** 37.

15. ATIH : Agence technique de l'information sur l'hospitalisation. 2022. https://www.atih.sante.fr/

16. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. *Springer New York* 2000; doi:10.1007/978-1-4757-3294-8

17. Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. *Stat Med* 2009; **28:** 2473–2489.

18. Royston P, Parmar MKB. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med* 2011; **30:** 2409–2421.

19. Uno H, Claggett B, Tian L, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. *J Clin Oncol Off J Am Soc Clin Oncol* 2014; **32:** 2380–2385.

20. Grafféo N, Latouche A, Geskus RB, Chevret S. Modeling time-varying exposure using inverse probability of treatment weights. *Biom J Biom Z* 2018; **60:** 323–332.

21. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med* 2014; **33:** 1242–1258.

22. Wyss R, Gagne JJ, Zhao Y, et al. Use of Time-Dependent Propensity Scores to Adjust Hazard Ratio Estimates in Cohort Studies with Differential Depletion of Susceptibles. *Epidemiol Camb Mass* 2020; **31:** 82–89.

23. Hernán MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med* 2002; **21:** 1689–1709.

24. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. *Stat Methods Med Res* 2017; **26:** 1654–1670.

25. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Stat Med* 2014; **33:**1685–1699.

26. Austin PC, Thomas N, Rubin DB. Covariate-adjusted survival analyses in propensity-score matched samples: Imputing potential time-to-event outcomes. *Stat Methods Med Res* 2020; **29:** 728–751.

Comparison of conservative and invasive approaches on one-year survival among critically ill elderly medical patients: nationwide observational study

(The OCTO-REVERSE Study)

STATISTICAL ANALYSIS PLAN

Version 1: December 2, 2019
Version 2: August 5, 2021
Reformatting for publication: 2023

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INTRODUCTION

SAP version and revision story

The statistical analysis plan was developed during the summer of 2021 during data collection (in two meetings: June 10, 2021, and August 5, 2021, with numerous exchanges in between), before having full access to the study database.

It was structured as an extension of the scientific protocol (also attached, drafted in French on December 2, 2019, which is actually the first version of the statistical analysis plan). The main differences between these two versions are:

- The exclusion of renal replacement therapy as a variable of interest (due to coding biases between acute and chronic situations)
- The enhanced statistical evaluation, specifically considering Time-to-Event analyses, with the collaboration of Philippe Aegerter, as senior statistician.

The current document was written after accessing the database and analyzing the data, it has been drawn up in accordance with the guidelines provided by the study: *Hiemstra B, Keus F, Wetterslev J et al. DEBATE-statistical analysis plans for observational studies. BMC Med Res Methodol 19, 233 (2019). https://doi.org/10.1186/s12874-019-0879-5*

We certify that this SAP is adequate in scope of the main analyses of the Octo-Reverse study.

Project number and human subjects protection review boards

- Local project number (scientific protocol) : Committee of Expertise for Research, Studies, and Evaluations in the Health Field: **CEREES Registration: 962976** (April 23, 2020)
- Independent national data protection authority: **CNIL Registration: 920181** (May 11, 2020)
- Independent institutional review board: **IRB Registration: #00011928** (August 19, 2022)

Background and rationale

The Covid-19 pandemic highlighted older age as a strong factor associated with death, raising again the question of the relevance of critical care for elderly patients. Regardless of the pandemic, the heterogeneity of studies on this issue brought one-year survival rate after intensive care unit (ICU) admission to about 50% for older patients. This absolute uncertainty could have favored decision-making process based on clinical judgment alone while triage-systems based even on limited evidence would have been ethically preferable. In addition, overoptimistic expectations of outcome could have favored the increasing proportion of elderly patients admitted to ICU and the enhancement of time-limited trial approach for invasive treatments, which a part turned out to be disproportionate. After correcting for the growing frailty that accompanies aging, those studies showed main factors of poor prognosis: older age (≥ 80 years), non-operative condition and exposition to an invasive procedure. By performing a nationwide study, we will seek to assess characteristics, management and outcomes for elderly-ICU patients after the combination of these three factors.

METHOD

Research hypothesis

The null hypothesis is that there is no true association between any single use or a combination of invasive procedures (invasive approach vs, on the contrary, conservatice approach) and prognosis of older patients admitted for medical reason in ICUs.

The alternative hypothesis is that there is an association between invasive approach and prognosis.

Study objectives

The primary objective of this study is to determine the association between the use of an invasive procedure during the ICU stay and one-year survival starting from the date of ICU admission.

Secondary objectives are to explore the association between the use of an invasive procedure during the ICU stay and:

- Overall Mortality Rate at 28, 90 and 365 days
- Overall Mortality Rate in ICU and in hospital
- Length of ICU stay and hospital stay
- ICU readmission rate at one year

Study design

The Octo-Reverse study is a retrospective analysis of data prospectively collected in the Système National des Données de Santé (SNDS), the national French healthcare database. The entire study is purely observational in design; no interventions were applied as part of the study protocol.

Sampling

Being an observational study, there is no randomization of patients. All patients and stays responding to selection criteria were used without

Framework

All outcomes are tested for superiority

Sample size, power and detectable association

Previous studies examining the prognosis of very old patients in the ICU have shown variability across different countries, settings, selection criteria, analyzed factors, and time horizons. Few studies specifically addressed the impact of invasive procedures. Of particular relevance is the study by Atramont et al. which investigated 2013 French ICU patients and calculated odds ratios (OR) for in-hospital death associated with invasive mechanical ventilation (2.42; 95% CI [2.25-2.62]) and vasopressor support (2.63; 95% CI [2.45,2.83]), while the ORs for 3-month mortality after hospital discharge were much lower (1.08 [0.97-1.21] and 1.30 [1.16-1.45], respectively). Similarly, Ferrante et al. reported in their 1998-2012 US monocentric study that mechanical ventilation was strongly associated with 1-year mortality (adjusted Hazard Ratio, 2.89; 95% CI [1.91-4.37]).

During the year 2013, Atramont identified 23,283 patients aged 80 or older, with nearly 45% being surgical (including trauma and burn injuries) patients, resulting in approximately 10,000 patients per year. However, intermediate and step-down units were not included in their analysis. Among these older patients, approximately 56% received mechanical ventilation. Mortality rates were 30.4% and 61.7% for in-hospital and 3-year post-discharge, respectively. Fassier et al. reported an in-hospital mortality rate of 33.9% among the 32,844 French ICU hospitalizations in 2009, while the monocentric study by Roch et al. found a higher rate of 55%. Seethala et al. reported a 1-year mortality rate of 32.8% among 10,583 US patients, whereas Roch (15) found a rate of 72%.

For our study, we anticipate including at least 15,000 patients each year. Our main analysis will focus on mechanical ventilation as an example for our power calculation. Assuming that the 1-year mortality rate among controls ranges from 0.3 to 0.5, and the risk ratio associated with this procedure is at least 1.1, a global sample size of 3200 (for a mortality rate of 0.5) to 7600 (for a mortality rate of 0.3) will provide 80% power to detect this effect. Additionally, patient matching based on propensity score will increase power. Lastly, as we are interested in potential trends in patient trajectories, our dataset will encompass multiple years.

Timing of final analyses

Data cleansing will be performed upon retrieval of the selected dataset. The final analysis will be conducted hereafter.

Timing of outcome assessment

Death certificates are continuously collected by Cepi-DC, using an automated procedure, followed by checks. The coding of causes of deaths is made by experts, so the detailed update of the SNDS database is within 6 to 12 months.

In our dataset, follow-up of patients without a death record will be censored at a date corresponding to the 95th percentile of all dates of death.

STATISTICAL PRINCIPLES

Confidence interval and p-values

In this prognostic study, there is a single primary outcome, and therefore, no adjustment will be made for multiplicity. For the secondary objectives, all relevant statistical tests will be two-sided and conducted at a significance level of 0.05. Additionally, all reported confidence intervals will be 95% and two-sided.

Adherence and Protocol deviations

As the study is strictly observationnal and aims to summarise what is the “real life” of older patients in ICUs, protocol deviations are not applicable.

Analysis sets

The analysis population is defined based on the recorded ICU procedures in the database. This means that the individuals included in the analysis sets are defined “as treated” and selected according to the specific treatments and interventions they received during their ICU stay, as documented in the database.

STUDY POPULATION

Screening and eligibility

Eligible patients who were not included will be compared to included patients by comparing their general characteristics (age, sex, year of admission), and SAPS-II scores. All eligible patients will be included on their first day of ICU admission, whatever the duration of the ICU stay or the level or the ICU (intermediate or step-down unit).

Inclusion criteria

- Age at ICU admission ≥ 80 years
- ICU admission during the period January 2013- December 2018
- Non-operative condition, defined as no surgical procedure or no surgical DRG, either during the hospitalization encompassing the index ICU stay or during the 30 days before this ICU admission

Exclusion criteria

Any of the following:

- Any missing data on the following core dataset : age, sex, SAPSII, main diagnosis, procedures (code and timing), dates (admission, discharge, follow-up), DRG code
- DRG error

Data Retrieval

During the preparation of this SAP, the retrieval of data was still in progress. To comply with our request and French regulations on data confidentiality, the SNDS data managers have deposited a subset of the entire database into a dedicated secure workspace. This subset specifically includes individuals who were admitted to an intensive care unit (including intermediate and step-down units) at least once between 2009 and 2018 and were aged 80 or above at the time of admission.

Given the structure of the database, the following steps are necessary:

- Removal of hospital stays with erroneous DRG codes, utilizing a key that combines the year of discharge, hospital code, and stay code within the hospital and year.
- Concatenation of hospital stays for the same patient across time, organizing them by entry date and calculation of the time interval between successive stays.
- Association of each hospital stay with its corresponding elementary stays in different units to generate an array of unit stays, ordered by entry time in a wide format.
- Calculation of the duration of each unit stay, particularly in the ICU.
- Linkage of the table of procedures (including procedure codes, number of executions, and start and stop dates within the hospital stay) to the table of hospital stays using the stay key, resulting in an array of procedures ordered by their start time in a wide format.
- Identification of hospital stays with surgical procedures.
- Determination of the unit where each procedure was performed.
- Calculation of the start time and total duration of invasive procedures (such as invasive ventilation and vasopressor support) within the ICUs.
- Connection of the table of secondary diagnoses (ICM10 codes) to the table of hospital stays using the stay key to obtain an array of ICM10 codes, ordered by the units where they were attributed.
- Linkage of the table of hospitals (including information on public/private funding, university status, equipment, geriatric or palliative care facilities) to the table of hospital stays using the hospital code.
- Association of the resulting table of documented stays with the table of patients to retrieve social insurance status, date, and cause of death.
- To ensure homogeneity, exclusion of the years 2009-2012 due to modifications in the structure of some tables or the recording of SAPSII.
- Chronological arrangement of the stays, and selection of the first hospital stay where each patient was admitted to an ICU for non-surgical reasons, provided they were 80 years or older.

A STROBE flow diagram will be used to illustrate the progression of patients throughout the study, from the initial screening for eligibility in the database to the partitioning based on ICU procedures and the one-year follow-up. Additionally, we will summarize the number of exclusions, along with the reasons for their exclusion.

Withdrawal or lost to follow-up

The study is a retrospective analysis of data already collected in the SNDS. Recording of hospitalization data is mandatory in the SNDS. Therefore, the concept of withdrawal or lost for follow-up cannot be applied.

Baseline characteristics

The following information will be collected at the time of ICU admission:

- Age (in years)
- Gender
- Social status and place of residence
- Simplified Acute Physiology Score (SAPS) II at ICU admission
- Pre-existing medical conditions and diagnoses (which will be used to calculate the Charlson's comorbidity score)
- Reason for ICU admission
- Dates of hospital and ICU admission
- Pre-admission location (such as home, emergency department, another unit, or another hospital)
- Characteristics of the hospital and ICU (funding, university affiliation, level of care)

We will present these characteristics in a baseline characteristics table. Continuous variables will be summarized using either the mean and standard deviation (SD) or the median and interquartile range (IQR) for variables with asymmetric distribution. The normality of continuous data will be assessed through Q-Q plots and histograms. Categorical variables will be described by the proportion of participants in each category, along with 95% confidence intervals (CIs) when applicable.

ICU daily follow-up

- Vital status
- Hospital and ICU discharge or readmission (date, pre-admission location: home / emergency / other unit / other hospital, destination: home / other unit / other acute hospital / long-term care)
- Endotracheal intubation, extubation, re-intubation, tracheostomy
- Life-sustaining treatments. These procedures are date-stamped (relative to the start of the hospital stay) and coded using a national multidimensional classification system called CCAM
- Main diagnosis and secondary diagnoses (ICM10)

Long term follow-up

- Readmission to the hospital or ICU
- Vital status
- Causes of death, if applicable

We will extract mortality data at 30 days, 3 months, 1 year, and 5 years from the survival duration. Additionally, we will present the length of ICU and hospital stay, as well as readmission rates at one year

Exposure

The exposure variable will be defined as the first occurrence of either vasopressor support or invasive mechanical ventilation during the ICU stay. This will be referred to as the invasive approach, while the opposite will be referred to as the conservative approach. We make this choice because these procedures are reliably documented for urgent decision-making. We will not consider non-invasive ventilation and renal replacement therapy due to the ambiguity in coding between acute and chronic situations, and sometimes maintained as palliative support.

Assumed confounding covariates

The majority of variables measured in our study are inherently correlated, as they primarily pertain to a patient's physiological reserve or functional status. Unmeasured factors, such as environmental, genetic, or psychological influences, have the potential to confound our outcome variables. To address this, we provide an illustrative example of confounding variables and categorize them as either 'measured' or 'unmeasured'.

Mortality is presumed to be confounded by:

- Measured: age, sex, pre-existing comorbidities (Charlson), SAPS-II score, reason for admission, palliative care, preadmission location, and ICU or hospital characteristics (academic status)
- Unmeasured: respiratory and circulatory parameters, cause of mortality (e.g., death resulting from multi-organ failure, failure to rescue, do-not-resuscitate [DNR] orders, patient's or family's personal wishes, or a combination thereof), crowding or insufficient caregiver availability, ICU or hospital characteristics.

Length of stay is presumed to be confounded by:

- Measured: age, comorbidities (Charlson), SAPS-II score, palliative care, ICU or hospital characteristics
- Unmeasured: crowding or insufficient caregiver availability, ICU or hospital characteristics.

Hence, we acknowledge the presence of residual confounding in our dataset due to unmeasured confounding factors, some of which have been outlined above

ANALYSIS

Descriptive

All continuous variables, including changes from baseline, will be summarized globally and according to the ICU approach (invasive vs conservative) using means, standard deviations (SD), or medians and interquartile ranges for skewed variables. Categorical variables will be summarized globally and according to the ICU approach using counts and percentages, supplemented with 95% confidence intervals (CIs). The normality of distributions for quantitative variables will be assessed using Q-Q plots and histograms. For each variable, unless otherwise specified in advance, the choice of statistical tests and multivariate models (parametric or non-parametric) will be determined based on observed characteristics such as the normality of distributions and residuals, as well as collinearity. The relationship between a quantitative factor and any response will be explored by fitting fractional polynomials.

Primary end-point and time-to-event analysis

- Measurement of Survival and Follow-up

Survival will be assessed from the date of ICU admission until the date of death or until the last follow-up, in cases where the patient's data is no longer available. Since the data refreshment for SNDS (French healthcare data system) occurs periodically nationwide, the date of the last follow-up will be estimated using the 95th percentile of the recorded dates of death.

- Comparison of Mortality Proportions

The raw mortality rates at one year will be compared between the two ICU approaches using a Chi-squared test.

- Time-to-Event Analysis

The main comparison will be analyzed using a time-to-event approach, with a censoring time set at one year (365 days) from the first ICU admission. The description of mortality proportions will be presented using Kaplan-Meier survival curves when independent factors are binary (such as ICU approach or procedures), categorical (pre-admission location), or ordinal (either native, like the Charlson index, or resulting from dividing a continuous variable into groups, such as age groups).

- Immortal Time Bias

To address the issue of immortal time bias when comparing the survival of the invasive group (patients receiving vasopressor support or invasive mechanical ventilation) with the conservative group, the occurrence of an invasive procedure will be considered as a time-dependent covariate. The time of first use of any invasive procedure will be estimated and treated as a covariate in the analysis. To avoid ties, when the first invasive procedure and death occur on the same day, the time of death will be shifted by 0.1 day. Time-dependent Kaplan-Meier survival curves will be established following the approach proposed by *Steven M Snapinn, Qi Jiang & Boris Iglewicz (2005) Illustrating the Impact of a Time-Varying Covariate With an Extended Kaplan-Meier Estimator, The American Statistician, 59:4, 301-307, DOI: 10.1198/000313005X70371*

- Univariable Cox Proportional Hazard Regression Analysis

Associations between the incidence of death at one year and exposure or confounding factors will be explored using univariable Cox proportional hazard regression analysis. The relationship between a quantitative factor and the incidence of death will be examined by fitting fractional polynomials.

- Multivariable Analysis

Covariates with a p-value less than 0.2 in the univariable analysis will be included in the multivariable model. A multivariable analysis of the association between procedures or patient characteristics and outcomes will be performed using a Cox proportional hazards model. Hazard ratios (HR) will be calculated, and ties will be handled using the Efron approximation. The proportional hazards assumption will be assessed through plots of scaled Schoenfeld residuals and corresponding tests. If a time-varying effect is detected, the Cox model will be extended by adding an interaction term between the covariate and a transformation of time, with the choice of transformation determined by the Akaike Information Criterion (AIC).

- Propensity Score Analysis

Given the potential differences between patients receiving invasive support and those in the conservative group, a propensity score (PS) method will be employed to minimize confounding and obtain an unbiased estimate of the treatment effect. However, conventional PS methods may introduce bias when treatment or exposure varies over time. To address this issue, an inverse probability of treatment weighting (IPTW) method adapted to the time-dependent context will be used. The time span will be divided into strata, allowing the calculation of a propensity score at different time points. Propensity scores will be calculated using a Cox model that predicts the use of invasive procedures based on patient characteristics available at admission. Emphasis will be placed on balancing prognostically important covariates in the score.

- Validation of Propensity Score Weighting

Propensity score distributions will be examined to assess the overlap between the two groups before and after weighting. Variable balance will be assessed by examining standardized mean differences before and after weighting, variance ratios between the two groups, and the overlapping coefficient. Sensitivity analyses will be conducted by trimming weights at different percentiles.

- Estimation of Treatment Effects

IPTW will be used to estimate the average treatment effect (ATE) for the 1-year mortality associated with invasive support compared to the conservative approach. Hazard ratios (HR) and their 95% confidence intervals will be estimated. As weighting may modify the sample size relative to the original population and induce a lack of independence, a robust sandwich-type estimator will be used to calculate standard errors, accounting for this uncertainty. Regression adjustment will also be employed to address confounding variables used for stabilization.

- Summary of Results

When the treatment effect is time-varying, the overall hazard ratio (HR) will be interpreted as a weighted average HR over the event times. Additionally, the difference in the restricted mean survival time (RMST) will be calculated as a model-free parameter, providing a measure of the loss of life expectancy.

Sensitivity and subgroup analyses

We will conduct sensitivity analyses to evaluate the reliability of the overall hazard ratio (HR) associated with invasive procedures. These analyses will involve the following approaches:

- Trimming of ATT Weights: We will assess the impact of different trimming methods on the results. Specifically, we will examine the HR using propensity score weights that are trimmed at the 5th and 95th percentiles, as well as without any trimming.

- Time Strata Definition: The robustness of the results will be examined by defining time strata based on different criteria. We will consider time strata where each day an invasive procedure or a death occurred, as well as predefined periods.

In addition to the sensitivity analyses, the interpretation of the results will be enhanced by analyzing mortality at various follow-up times. We will assess mortality rates at 28 days from ICU admission, at one year from hospital discharge, as well as at 7 and 30 days.

Regarding subgroup analysis, we will divide the population into three subcohorts based on age: less than 85 years, 85 to less than 90 years, and 90 years or older. A Forest plot will be generated, presenting the estimated point and confidence intervals for the treatment effect across these age subgroups.

Secondary End-points

The secondary survival endpoints will be described and analyzed using the same methodology as the primary endpoint.

For the readmission rate, the data will be modeled as time-to-event, censored at 365 days (D365), within a competing risk framework. In this framework, readmission will be considered the main event, while death before readmission will be treated as a competing event. The time to each event, referred to as subdistribution hazards, will be modeled using a Fine & Gray model, with the type of ICU approach (invasive or conservative) included as a covariate. This analysis will provide a subdistribution hazard ratio (SHR), which takes into account both the time to readmission and the probability of death. Additionally, the length of ICU stay (in days) and the length of hospital stay will be compared between the two ICU approaches using a Wilcoxon test. These lengths will also be modeled using a linear model.

Missing Data

Since stays with any missing data on the core dataset will be excluded from the analysis, there is no need for imputation of missing data.

[Statistical software : All statistical analyses will be conducted using the SAS Enterprise Guide v7.15 (SAS Institute Inc., Cary, NC, USA) provided by the SNDS infrastructure].