OBJECTIVES: The determinants of decisions to limit life support (withholding or withdrawal) in ventilated stroke patients have been evaluated mainly for patients with intracranial hemorrhages. We aimed to evaluate the frequency of life support limitations in ventilated ischemic and hemorrhagic stroke patients compared with a nonbrain-injured population and to determine factors associated with such decisions.

DESIGN: Multicenter prospective French observational study.

SETTING: Fourteen ICUs of the French OutcomeRea network.

PATIENTS: From 2005 to 2016, we included stroke patients and nonbrain-injured patients requiring invasive ventilation within 24 hours of ICU admission.

INTERVENTION: None.

MEASUREMENTS AND MAIN RESULTS: We identified 373 stroke patients (ischemic, n = 167 [45%]; hemorrhagic, n = 206 [55%]) and 5,683 nonbrain-injured patients. Decisions to limit life support were taken in 41% of ischemic stroke cases (vs nonbrain-injured patients, subdistribution hazard ratio, 3.59 [95% CI, 2.78–4.65]) and in 33% of hemorrhagic stroke cases (vs nonbrain-injured patients, subdistribution hazard ratio, 3.9 [95% CI, 2.97–5.11]). Time from ICU admission to the first limitation was longer in ischemic than in hemorrhagic stroke (5 [3–9] vs 2 d [1–6] d; p < 0.01). Limitation of life support preceded ICU death in 70% of ischemic strokes and 45% of hemorrhagic strokes (p < 0.01). Life support limitations in ischemic stroke were increased by a vertebrobasilar location (vs anterior circulation, subdistribution hazard ratio, 1.61 [95% CI, 1.01–2.59]) and a prestroke modified Rankin score greater than 2 (2.38 [1.27–4.55]). In hemorrhagic stroke, an age greater than 70 years (2.29 [1.43–3.69]) and a Glasgow Coma Scale score less than 8 (2.15 [1.08–4.3]) were associated with an increased risk of limitation, whereas a higher nonneurologic admission Sequential Organ Failure Assessment score was associated with a reduced risk (per point, 0.89 [0.82–0.97]).

CONCLUSIONS: In ventilated stroke patients, decisions to limit life support are more than three times more frequent than in nonbrain-injured patients, with different timing and associated risk factors between ischemic and hemorrhagic strokes.

KEY WORDS: critical care; end-of-life care; intracerebral hemorrhage; ischemic stroke; subarachnoid hemorrhage

The prognosis of mechanically ventilated stroke patients is poor, with 1-year mortality rates ranging from 60% to 92% (1–5). In this subset of extremely severe cases with high fatality rates, a high incidence of...
limitation (withholding or withdrawal) of life support has been reported, ranging from 30% to 40% (6–8) compared with 9–14% in large multicenter observational studies in the general ICU population (9–15). Compared with nonbrain-injured critically ill patients, the decision to limit life support in brain-injured patients may have more serious consequences, as the continuation of organ support could result in months or years of life in a state of disability that may be against the patient’s wishes (16). Assessing long-term vital and functional outcomes in these patients is difficult, and current prognostic models are based on datasets including a significant proportion of patients with treatment restriction. In turn, these life support limitations affect the outcomes of the populations in which the models were developed (17).

The high incidence of life support limitation in mechanically ventilated stroke patients and the potential confounding impact on prognostication models suggest that determinants of limitation of life support should be thoroughly investigated. In this observational multicenter study, we sought to describe the incidence, timing, and factors associated with life support limitation in critically ill patients, with either ischemic or hemorrhagic stroke, requiring invasive mechanical ventilation (IMV).

MATERIALS AND METHODS

Patient Data Source

This observational cohort study was conducted using data from the French prospective multicenter (n = 28 ICUs) OutcomeRea database. Patients admitted between 2005 and 2016 were considered for this study. We chose 2005 as the beginning of the study period as important end-of-life legislation was acted in France that year (18). Per this law, withholding or withdrawal of treatments is authorized when they appear “useless, disproportionate or having no other effect than solely the artificial preservation of life.” However, the decision to withdraw or withhold a treatment from a patient unable to express their will has to consider the wishes they might have expressed through advance directives and/or the wishes of a trusted person or, last, of the family. Furthermore, before making any decision, physicians have to respect a collegial medical procedure. Finally, euthanasia in France remains illegal. The OUTCOMEREA database, described in previous publications (19), has been approved by the French Advisory Committee for Data Processing in Health Research and the French Informatics and Liberty Commission (registration number 8999262). The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University Hospital (Clermont-Ferrand, France), who waived the need for informed consent (Institutional Review Board number 5891). The datasets used during the current study are available from the corresponding author on reasonable request.

Study Populations and Definitions

The stroke population included all adult patients with acute stroke and requiring IMV within 24 hours of ICU admission. ICU stays were considered as related to acute stroke in cases of: 1) direct ICU admission following stroke onset or 2) ICU admission during the initial acute care hospital stay following stroke onset. We excluded patients without hospitalization reports. From the same ICUs where the stroke population was selected, we defined a nonbrain-injured population comprised of nonstroke adult patients requiring IMV within 24 hours of ICU admission and without admission diagnoses associated with brain injury: cardiac arrest, status epilepticus, meningitis/encephalitis, and traumatic brain injury. We also chose to exclude subdural hematomas from our analysis, as it was retrospectively difficult to ascertain their nontraumatic nature.

Intracranial hemorrhages (ICHs) and subarachnoid hemorrhages (SAHs) were merged as “hemorrhagic strokes” (20). Limitations of life support were categorized as either withholding or withdrawing. Withholding of life support was defined as a decision not to start or increase a life-sustaining intervention. Life-sustaining interventions comprised organ support (mechanical ventilation invasive or not, vasopressors and dialysis) and acute phase stroke therapies if there was a theoretical indication for it. Withdrawal of life support was defined as a decision to actively stop a life-sustaining intervention presently underway (21). If more than one limitation decision occurred for a single patient, the most active limitation (withdrawing > withholding) defined the limitation category. End-of-life outcomes were categorized as follows: 1) death without limitation if death occurred in absence of any decision to limit life support, 2) death following limitation if death occurred after any limitation of life support, and 3) brain death, in cases of documented
cessation of cerebral function (21). The severity of illness was graded at ICU admission with the use of the Simplified Acute Physiology Score II (22) and the Sequential Organ Failure Assessment (SOFA) score (23). The nonneurologic SOFA was defined as the SOFA score without the neurologic component. Coma was defined as a Glasgow Coma Scale (GCS) score less than 8 (24). We used the Charlson comorbidities index to assess the burden of comorbid conditions (25).

### Data Collection

Data were prospectively collected at admission and daily throughout the ICU stay, through an anonymized electronic case report form using Vigirea, Rhea, and e-Rhea software (OutcomeRea, Aulnay-sous-Bois, France). Long-term survival after hospital discharge was collected by each local investigator. We retrospectively collected the following data in medical charts: date of stroke, location, and acute phase therapy (i.e., thrombolysis or endovascular thrombectomy for ischemic strokes and neurosurgery or embolization for hemorrhagic strokes).

### Statistical Analysis

Quantitative variables are presented as medians, first and third quartiles and compared between groups with the Wilcoxon test. Qualitative variables are presented as frequencies and corresponding percentages and compared with the chi-square test or Fisher exact test, as appropriate.

To compare the risk of life support limitation between stroke and nonbrain-injured populations, we used an adjusted Fine and Gray subdistribution competing risk model (26) to estimate the subdistribution hazard of stroke as a class variable (ischemic stroke/hemorrhagic strokes/no stroke) and considering ICU death without limitation as the competing event. For each stroke subgroup, factors associated with the occurrence of a limitation of life support were evaluated using a Fine and Gray model (26), with the same competing event. All models were adjusted on clinically relevant factors or factors associated \( (p < 0.2) \) with the outcome of interest in univariate analysis. In the presence of collinear variables, the most clinically relevant one was retained. Variables were selected using a backward selection procedure with a threshold of \( p \) value of less than 0.1. The log-linearity of quantitative variables included in the models was tested. When this was not the case, variables were binarized using the median as the cutoff.

To account for variability in practice of life support limitation across ICUs (12, 27), models were stratified on center (centers with < 10% of the cohort were combined into one stratum). Two-by-two clinically relevant interactions were tested in each model. Missing data were all completely at random with less than 10% missing values per variable and were handled by simple imputation with the median/most frequent method (28). For each stroke subgroup, we conducted a sensitivity analysis by forcing in the models the period of study inclusion, arbitrarily divided into 4-year time intervals.

All statistical analyses were carried out with SAS 9.4 (SAS Institute, Cary, NC). A \( p \) value of 0.05 and lower was considered statistically significant.

### RESULTS

Among 17,520 ICU admissions over the study period, we identified 373 acute stroke patients from 14 ICUs where IMV was initiated within 24 hours of admission. In the same 14 ICUs, we identified 5,683 nonbrain-injured patients (Supplemental Fig. 1, Supplemental Digital Content 1 http://links.lww.com/CCX/A505). Stroke patients were predominantly male (59%), age 68.7 years (58.2–76.5 yr) old, with strokes classified as ischemic \( (n=167, 45%) \) and hemorrhagic \( (n=206, 55%) \). The reasons for intubation and mechanical ventilation were coma \( (n=271, 73%) \), respiratory failure \( (n=46, 12%) \), seizures \( (n=27, 7%) \), cardiac arrest \( (n=17, 5%) \), and elective procedure \( (n=12, 3%) \). Patients’ characteristics according to stroke type or absence of brain injury are presented in Table 1. Ischemic stroke patients were admitted to university hospitals in 92 of 167 cases (55%), hospitals with a stroke unit in 160 of 167 cases (96%), and hospitals with a neurosurgery unit and interventional radiology in 80 of 167 cases (48%). Hemorrhagic stroke patients were admitted to university hospitals in 131 of 206 cases (64%), hospitals with a stroke unit in 160 of 167 cases (96%), and hospitals with a neurosurgery unit and interventional radiology in 107 of 206 cases (48%).

During their ICU stay, 137 of 373 stroke patients (37%) and 695 of 5,683 nonbrain-injured patients (12%) underwent a limitation of life support. The frequency of such limitation was 41% (69/167 patients) for ischemic strokes and 33% (68/206 patients) for hemorrhagic strokes \( (p = 0.1) \). In a Fine and Gray subdistribution multivariable competing risk model
adjusted on age, comorbidities, and severity at ICU admission, we found that having an ICU admission diagnosis of ischemic stroke was associated with a 3.6-fold increased (95% CI [2.78—4.65]) risk of undergoing a limitation of life support, as compared to the nonbrain-injured population. Similarly, having an ICU admission diagnosis of hemorrhagic stroke was associated with a 3.9-fold increased (95% CI [2.97—5.11]) risk of qualifying for limitation of life support, as compared to the nonbrain-injured population.

**TABLE 1.**
Population Characteristics According to Stroke Subtype or Absence of Brain Injury

| Variables                                           | Nonbrain-Injured Patients, n = 5,683 | Ischemic Stroke Patients, n = 167 | Hemorrhagic Stroke Patients<sup>ab</sup>, n = 206 | p<sup>b</sup> |
|-----------------------------------------------------|--------------------------------------|----------------------------------|-----------------------------------------------|------------|
| Demographics/history                                 |                                       |                                  |                                               |            |
| Age, yr, median (quartile 1–quartile 3)             | 62.4 (49.4–74)                       | 69.6 (61.2–77.2)                 | 67 (56.6–76.4)                               | 0.09       |
| Male sex, n (%)                                      | 3,506 (61.7)                         | 112 (67.1)                       | 109 (52.9)                                   | < 0.01     |
| Charlson comorbidity index ≥ 1, n (%)               | 3,810 (67)                           | 103 (61.7)                       | 97 (47.1)                                    | < 0.01     |
| ICU characteristics                                  |                                       |                                  |                                               |            |
| University affiliated ICU, n (%)                    | 3,846 (67.7)                         | 92 (55.1)                        | 131 (63.6)                                   | 0.10       |
| Glasgow Coma Scale score at admission, median (quartile 1–quartile 3) | 12 (5–15)                            | 6 (3–10)                         | 3 (3–6)                                      | < 0.01     |
| Simplified Acute Physiology Score II, median (quartile 1–quartile 3) | 50 (37–64)                           | 56 (45–67)                       | 61 (52–77)                                   | < 0.01     |
| ICU length of stay, d, median (quartile 1–quartile 3) | 6 (3–13)                             | 7 (4–13)                         | 3 (2–8)                                      | < 0.01     |
| Life support limitations                             |                                       |                                  |                                               |            |
| Any life support limitation<sup>c</sup>, n (%)      | 695 (12.2)                           | 69 (41.3)                        | 68 (33)                                      | 0.10       |
| Limitation categories<sup>c</sup>, n (%)            |                                       |                                  |                                               | < 0.01     |
| Withholding                                         | 504 (8.9)                            | 31 (18.6)                        | 16 (7.8)                                     | .          |
| Withdrawal                                          | 314 (5.5)                            | 38 (22.8)                        | 52 (25.2)                                    | .          |
| Time from ICU to first limitation, d, median (quartile 1–quartile 3) | 6 (2–15)                             | 5 (3–9)                          | 2 (1–6)                                      | < 0.01     |
| Outcomes, n (%)                                     |                                       |                                  |                                               |            |
| ICU mortality                                        | 1,322 (23.3)                         | 92 (55.1)                        | 145 (70.4)                                   | < 0.01     |
| End-of-life outcome                                  |                                       |                                  |                                               | < 0.01     |
| Brain death                                         | 0                                    | 21 (22.8)                        | 68 (46.9)                                    | .          |
| Death without limitation of life support             | 755 (57.1)                           | 7 (7.6)                          | 12 (8.3)                                     | .          |
| Death following a limitation of life support         | 567 (42.9)                           | 64 (69.6)                        | 65 (44.8)                                    | .          |

<sup>a</sup>Intracranial hemorrhage and subarachnoid hemorrhage. <sup>b</sup>Comparison of acute ischemic stroke patients and hemorrhagic stroke patients. <sup>c</sup>If more than one limitation of life support occurred, the most active limitation (withdrawing > withholding) defined the limitation category.
Among patients who underwent life support limitation, withdrawal was the predominant limitation category in the stroke population (ischemic strokes, 38/69 [55%]; hemorrhagic strokes, 52/68 [76%]), whereas withholding was the most frequent category in the non-brain-injured population (381/695 [55%]). The daily ICU incidence rate of life support limitation according to stroke subtype or absence of brain injury is presented in Figure 1 and shows different time patterns between stroke and non-brain-injured patients. Time from ICU admission to the first limitation of life support was the shortest in hemorrhagic stroke, both compared with ischemic strokes (2 [1–6] vs 5 d [3–9 d]; \(p < 0.01\)) and non-brain-injured patients (2 [1–6] vs 6 d [2–15 d]; \(p < 0.01\)).

There was no difference in time from ICU admission to the first limitation between ischemic stroke non-brain-injured patients (5 [3–9] vs 6 d [2–15 d]; \(p = 0.67\)).

ICU mortality was 92 of 167 (55%), 145 of 206 (70%), and 1,322 of 5,683 (23%) for ischemic stroke, hemorrhagic stroke, and non-brain-injured populations, respectively (Table 1). In the non-brain-injured population, death following life support limitation occurred in 567 of 1,322 cases (43%) (Table 1). In the stroke population, death following a limitation of life support occurred in 129 of 237 (54%) patients, including 64 of 92 ischemic stroke patients (70%) and 65 of 145 hemorrhagic stroke patients (45%) (\(p < 0.01\)). Brain death occurred in 21 of 92 ischemic stroke patients (23%) and 68 of 145 hemorrhagic stroke (47%) (\(p < 0.01\)).

End-of-life outcomes according to the time from ICU admission and by stroke subtype are presented in Figure 2. From the fifth day of ICU stay and beyond, the rate of death following life support limitation exceeded 80% in ischemic stroke patients and 70% in hemorrhagic stroke patients.

Univariate analysis of factors associated with any life support limitation is presented in Table 2 (for univariate analysis by stroke subset see Supplemental Tables 2 and 3, Supplemental Digital Content 1, http://links.lww.com/CCX/A505). In the subset of ischemic stroke patients, variables significantly associated with a decision to limit life support in multivariate analysis were stroke location (vertebrobasilar vs anterior circulation location, subdistribution hazard ratio [sHR], 1.61 [1.01–2.59]) and a modified Rankin score greater than 2 before stroke onset (sHR, 2.38 [1.27–4.55]) (Fig. 3).

In the subset of hemorrhagic stroke patients, variables independently associated with a decision to limit life support in multivariate analysis were age greater than 70 years (sHR, 2.29 [1.43–3.69]), a GCS score less than 8 at ICU admission (sHR, 2.15 [1.08–4.3]), and the nonneurologic SOFA score at ICU admission (sHR, 0.89 [0.82–0.97]) (Fig. 3). The period of inclusion in the study, when forced into each model, was not significantly associated with a decision to limit life support (Supplemental Tables 4 and 5, Supplemental Digital Content 1, http://links.lww.com/CCX/A505). Among the 137 patients with a limitation of life support, univariate analysis of factors associated with a choice of withholding rather than withdrawal of life support is presented in the Supplemental Table 6 (Supplemental Digital Content 1, http://links.lww.com/CCX/A505).
Figure 2. End-of-life outcome according to length of ICU stay (d): comparison between nonbrain-injured patients and stroke subtypes. 
A. Nonbrain-injured patients. B. Ischemic stroke patients. C. Hemorrhagic stroke patients.
| Variables                                      | Limitation of Life Support |  |  |  |
|------------------------------------------------|----------------------------|---|---|---|
|                                                 | No Limitation, \( n = 236 \) | Any Limitation, \( n = 137 \) |  |  |
| Demographics/history                            |  |  |  |  |
| Age, yr, median (quartile 1–quartile 3)         | 65.5 (56.3–74.1)            | 72.8 (62.6–79.6) | < 0.01 |  |
| Male sex, \( n \) (%)                          | 134 (56.8)                  | 87 (63.5) | 0.20 |  |
| Charlson comorbidity index \( \geq 1 \), \( n \) (%) | 120 (50.8)                  | 80 (58.4) | 0.16 |  |
| Hospital characteristics, \( n \) (%)           |  |  |  |  |
| University hospital                             | 137 (58.1)                  | 86 (62.8) | 0.37 |  |
| Stroke unit on-site                             | 220 (93.2)                  | 122 (89.1) | 0.16 |  |
| Neurosurgery unit on-site                       | 119 (50.4)                  | 68 (49.6) | 0.88 |  |
| ICU type                                        |  |  |  |  |
| Medical                                         | 129 (54.7)                  | 79 (57.7) | 0.64 |  |
| Mixed                                           | 104 (44.1)                  | 55 (40.1) |  |  |
| Surgical                                        | 3 (1.3)                     | 3 (2.2) |  |  |
| ICU authorized for organ donation                | 161 (68.2)                  | 84 (61.3) | 0.18 |  |
| Ischemic stroke characteristics (\( n = 167 \)) |  |  |  |  |
| Location, \( n \) (%)                          |  |  |  | 0.11 |
| Anterior circulation                            | 67/98 (68.4)                | 38/69 (55.1) |  |  |
| Vertebrobasilar circulation                     | 31/98 (31.6)                | 31/69 (44.9) |  |  |
| Acute phase therapy*, \( n \) (%)               | 26/98 (26.5)                | 8/69 (11.6) | 0.02 |  |
| Time from stroke to ICU admission, d, median (quartile 1–quartile 3) | 2 (1–7)                    | 1 (1–2) | 0.02 |  |
| Hemorrhagic stroke \(^b\) characteristics (\( n = 206 \)) |  |  |  |  |
| Location, \( n \) (%)                          |  |  |  | 0.62 |
| Deep                                            | 32/138 (23.2)               | 14/68 (20.9) |  |  |
| Lobar                                           | 85/138 (61.6)               | 40/68 (58.8) |  |  |
| Infratentorial                                  | 21/138 (15.2)               | 14/68 (20.6) |  |  |
| Acute phase therapy*, \( n \) (%)               | 27/138 (19.6)               | 7/68 (10.3) | 0.09 |  |
| Time from stroke to ICU admission, d, median (quartile 1–quartile 3) | 1 (1–2)                    | 1 (1–1) | 0.09 |  |

(Continued)
DISCUSSION

In this reanalysis of a prospective database, including 6,056 critically ill patients requiring mechanical ventilation within 24 hours of admission, we showed that 37% of stroke patients (n = 373) underwent life support limitation, representing more than a three-fold increase in the risk of receiving a decision to limit life support compared with nonbrain-injured patients (n = 5683). Although there was no difference in the global risk of limitation of life support between ischemic and hemorrhagic strokes, limitations occurred earlier in hemorrhagic stroke patients. Factors associated with life support limitation differed between stroke types, including mainly stroke location and pre-stroke modified Rankin score for ischemic strokes and mainly age and organ failure for hemorrhagic strokes.

The 37% rate of life support limitation observed in our cohort is consistent with rates reported in previous studies conducted in ICH patients, ranging from 34% to 43% (7, 8). Of note, our study provides unique data regarding the limitation rate in the specific population of ischemic stroke patients requiring IMV. Furthermore, we present accurate estimates, as they integrate the competitive risk of dying without receiving a decision of limitation. These models are particularly relevant in populations with very high case fatality rates where death precludes the occurrence of the outcome of interest (26, 29). Our results confirm that stroke patients under IMV are a population submitted to a high incidence of end-of-life decisions and thus deserve a more thorough evaluation (16, 30).

A prospective multicenter study investigating 1-year outcomes, ethical issues, and care pathways of acute stroke patients requiring IMV in the ICU is ongoing (NCT 03335995) (31).

We found that 54% of stroke patient ICU deaths and 43% of those of nonbrain-injured patients were preceded by a decision to limit life support. These rates are consistent with those reported in the general ICU population, ranging from 47% to 53% (10, 15, 32). When evaluating end-of-life outcomes by stroke subtype, it is interesting to note that ischemic stroke patients had a higher proportion of death following a decision to

| Variables | Limitation of Life Support | No Limitation, n = 236 | Any Limitation, n = 137 | p |
|-----------|----------------------------|------------------------|------------------------|---|
| ICU characteristics | | | | |
| Glasgow Coma Scale score at admission, median (quartile 1–quartile 3) | 5 (3–9) | 3 (3–6) | < 0.01 |
| Simplified Acute Physiology Score II, median (quartile 1–quartile 3) | 56 (45–68.5) | 65 (53–77) | < 0.01 |
| Duration of mechanical ventilation, d, median (quartile 1–quartile 3) | 3 (2–8) | 5 (2–8) | 0.02 |
| Vasopressor support, n (%) | 127 (53.8) | 52 (38) | < 0.01 |
| ICU length of stay, d, median (quartile 1–quartile 3) | 4 (2–11) | 6 (3–9) | 0.24 |
| Outcomes, n (%) | | | | |
| ICU mortality | 108 (45.8) | 129 (94.2) | < 0.01 |
| Hospital mortality | 126 (53.4) | 134 (97.8) | < 0.01 |
| 1 yr mortality | 138/215 (64.2) | 136/136 (100) | < 0.01 |

*Thrombolysis or endovascular thrombectomy. Intracranial hemorrhage and subarachnoid hemorrhage. Neurosurgery or embolization. Twenty-two of 373 stroke patients (6%) were lost to follow-up and censored at 47 d (23–153 d).
limit life support than hemorrhagic stroke patients, probably because hemorrhagic stroke patients had a higher proportion of brain death.

The highest incidence of life support limitation during ICU stay occurred during the first 4 days. For hemorrhagic strokes in particular, the incidence of limitation was highest within the 48 hours following ICU admission, with a more than two-fold incidence than any other period of the ICU stay. This result could notably be explained by a higher rate of direct ICU admission from home or the emergency department in hemorrhagic stroke patients, where physicians might initiate IMV without knowing neither the patient’s medical history nor the extent of brain injury. Early decisions of life support limitation have been associated with a higher risk of short-term mortality independently of patient factors, suggesting that some of these decisions may be undue (7, 8, 33). Inappropriate prognostic pessimism and premature limitations of life support define the mechanism by which self-fulfilling prophecies occur (34). Unfortunately, the design of our study and available data did not allow us to neither quantify the effect of self-fulfilling prophecies nor explore further this issue. Currently, life support limitation within 48

### Figure 3

Fine and Gray subdistribution hazard analysis for the occurrence of life support limitations, and death without such limitation as the competing event. **A**, Ischemic stroke patients. **B**, Hemorrhagic stroke patients. amodified Rankin Score, bversus anterior circulation location, cthrombolysis or endovascular thrombectomy, dper SOFA point. HR = hazard ratio, sHR = subdistribution hazard ratio, SOFA = Sequential Organ Failure Assessment.

| Variable                                      | Subdistribution HR | sHR [95% CI]  | p   |
|-----------------------------------------------|--------------------|---------------|-----|
| Pre-stroke mRS > 2 a                         |                    | 2.38 [1.27 - 4.55] | < 0.01 |
| Vertebrobasilar location b                    |                    | 1.75 [1.08 - 2.85] | 0.02 |
| Glasgow coma score < 8                        |                    | 1.54 [0.94 - 2.52] | 0.08 |
| Acute phase stroke therapy c                  |                    | 0.50 [0.24 - 1.05] | 0.07 |

| Variable                                      | Subdistribution HR | sHR [95% CI]  | p   |
|-----------------------------------------------|--------------------|---------------|-----|
| Age > 70 years                                 |                    | 2.26 [1.40 - 3.64] | < 0.01 |
| Glasgow coma score < 8                        |                    | 2.08 [1.06 - 4.07] | 0.03 |
| Male sex                                      |                    | 1.52 [0.98 - 2.38] | 0.06 |
| Non-neurologic SOFA at admission d            |                    | 0.89 [0.82 - 0.97] | < 0.01 |
| Time from stroke to ICU > 1 day               |                    | 0.59 [0.32 - 1.07] | 0.08 |
hours of ICU admission is not recommended in ICH patients (35), and time-limited ICU trials should be proposed in severe stroke patients. Bias that may result in underuse of life support in severe stroke patients include erroneous prognostic estimates (36–38), misunderstanding patient’s values and expectation (39) and undervaluing the future patient's health state (disability paradox) (30, 40). The influence of cognitive bias in the decision-making process must also be acknowledged and may be as important as patient factors (41).

The most commonly described risk factors for receiving a decision to limit life support in the general ICU population are age, the presence of chronic diseases, and clinical severity at ICU admission (11–13, 42, 43). In critically ill brain-injured patients, age and a low GCS are the most frequently reported (6, 44). It is interesting to note that in our study, risk factors appear to differ between ischemic and hemorrhagic stroke patients. For the latter, the usual patient-related risk factors were found (i.e., age and neurologic severity), with the notable addition of nonneurologic organ failure that appeared to play a protective role. We hypothesize that intensivists would be more inclined to continue aggressive care in these patients because nonneurologic organ failure may be more reversible and without obvious impact on functional outcome, as compared to neurologic failure. For ischemic stroke patients, however, neither age nor comorbidities were associated with life support limitation. We hypothesize that age and comorbidities are variables strongly associated with a decision of life support limitation even before referring the patients to an ICU (i.e., left censoring) and that this phenomenon may have mitigated the effect of these variables in our dataset (45, 46).

The strengths of our study include a multicenter population from a high-quality prospective database. The relatively small number of patients included, considering the study period and the 14 ICUs, is due to the fact that several ICUs did not contribute throughout the 12 years, and some used only a fraction of their beds to feed the database. Our study also has limitations. First, the OUTCOMEREA database was not built specifically for stroke studies, and all data regarding stroke are retrospective, collected from hospitalization records. As a result, specific severity scores are lacking: National Institutes of Health Stroke Scale (47) for ischemic strokes, ICH score for ICHs (48), and World Federation of Neurosurgical Societies or Hunt and Hess scores (49, 50) for SAH. For the same reason, data regarding the modality of treatments withheld or withdrawn, the reason for undertaking a life support limitation, and the presence or absence of advanced directives were not available. Second, end-of-life decision-making is a complex process, and we did not explore all the determinants that lead to a limitation of life support, which may include patient- or surrogate-centered determinants and physicians’ determinants (personal beliefs, religion, medical specialty, etc.) (16, 30). Third, our study population excluded stroke patients that were critically ill but were not referred to the ICU because of care-limiting decisions made by the neurologist or the emergency physician in charge. Fourth, when analyzing hemorrhagic strokes, we decided to merge ICH and SAH patients for analytical purposes. Although merging these two clinical entities has previously been done in the literature (20), a separate analysis of ICH and SAH could have brought additional information. Fifth, our results and conclusion may apply only for the setting and culture we recruited the patients from, as this is an exclusively French cohort including only medical and mixed ICUs. As only 50% of the cohort were treated with on-site neurosurgery and interventional radiology, we may have selected a population with a high proportion of patients not eligible for acute phase stroke therapy. However, as all multivariate models were stratified on centers of inclusion, we believe that this effect was accounted for. Sixth, due to the recent rise of mechanical thrombectomy following the publication of important randomized controlled trials (51–53), the current proportion of stroke patients intubated for an elective procedure is likely to be higher than reported in our study, thus limiting the generalizability of our results. Seventh, data on functional outcomes in survivors could not be reported despite being a more relevant endpoint than mortality for stroke studies.

**CONCLUSIONS**

In this secondary data use of a prospective multicenter cohort study of critically ill patients requiring IMV, we showed that life support limitation was more than three times more frequent in stroke patients than in nonbrain-injured patients. There were significant differences in timing and risk factors for limitation of life support between ischemic and hemorrhagic strokes. In ventilated stroke patients, early decisions to limit life support are frequent, and a high proportion of deaths
follow such decisions. These findings warrant further investigations to clarify the impact of life support limitation on prognostication models.

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REFERENCES

1. Santoli F, De Jonghe B, Hayon J, et al: Mechanical ventilation in patients with acute ischemic stroke: Survival and outcome at one year. Intensive Care Med 2001; 27:1141–1146
2. Schielke E, Busch MA, Hildenhagen T, et al: Functional, cognitive and emotional long-term outcome of patients with ischemic stroke requiring mechanical ventilation. J Neuro/2005; 252:648–654
3. Milhaud D, Popp J, Thouvenot E, et al: Mechanical ventilation in ischemic stroke. J Stroke Cerebrovasc Dis 2004; 13:183–188
4. de Montmollin E, Terzi N, Dupuis C, et al; OUTCOMEREA Study Group: One-year survival in acute stroke patients requiring mechanical ventilation: A multicenter cohort study. Ann Intensive Care 2020; 10:53
5. Sonneville R, Gimenez L, Labreuche J, et al: What is the prognosis of acute stroke patients requiring ICU admission? Intensive Care Med 2017; 43:271–272
6. Diringer MN, Edwards DF, Aiyagari V, et al: Factors associated with withdrawal of mechanical ventilation in a neurology/neurosurgery intensive care unit. Crit Care Med 2001; 29:1792–1797
7. Zahuranec DB, Brown DL, Lisabeth LD, et al: Early care limitations independently predict mortality after intracerebral hemorrhage. Neurology 2007; 68:1651–1657
8. Creutzfeldt CJ, Becker KJ, Weinstein JR, et al: Do-not-attempt-resuscitation orders and prognostic models for intraparenchymal hemorrhage. Crit Care Med 2011; 39:158–162
9. Azoulay E, Metnitz B, Sprung CL, et al; SAPS 3 investigators: End-of-life practices in 282 intensive care units: Data from the SAPS 3 database. Intensive Care Med 2009; 35:623–630
10. Ferrand E, Robert R, Ingrand P, et al; French LATAREA Group: Withholding and withdrawal of life support in intensive-care units in France: A prospective survey. French LATAREA group. Lancet 2001; 357:9–14

11. Wunsch H, Harrison DA, Harvey S, et al: End-of-life decisions: A cohort study of the withdrawal of all active treatment in intensive care units in the United Kingdom. Intensive Care Med 2005; 31:823–831

12. Quill CM, Ratcliffe SJ, Harhay MO, et al: Variation in decisions to forgo life-sustaining therapies in US ICUs. Chest 2014; 146:573–582

13. Lobo SM, De Simoni FHB, Jakob SM, et al; ICON investigators: Decision-making on withholding or withdrawing life support in the ICU: A worldwide perspective. Chest 2017; 152:321–329

14. Lautrette A, Garrouste-Orgeas M, Bertrand PM, et al; Outcomerea Study Group: Respective impact of no escalation of treatment, withholding and withdrawal of life-sustaining treatment on ICU patients' prognosis: A multicenter study of the outcomerea research group. Intensive Care Med 2015; 41:1763–1772

15. Lesieur O, Leloup M, Gonzalez F, et al; EPILAT study group: Withholding or withdrawal of treatment under French rules: A study performed in 43 intensive care units. Ann Intensive Care 2015; 5:56

16. Geurts M, Macleod MR, van Thiel GJ, et al: From directed care to physician’s predictions of short-term survival: A comparison between unassisted decision-making and the French model. JAMA 2014; 311:1629–1638

17. Veuillet-Bond M, de Kort FAS, de Kort PLM, et al: Predictive accuracy of the SOFA score in critical care: A systematic review. Intensive Care Med 2015; 41:1763–1772

18. Baumann A, Audibert G, Claudot F, et al: Ethics review: End of life legislation—the French model. Crit Care 2009; 13:204

19. Truche AS, Darmon M, Bailly S, et al; OUTCOMEREA Study Group: Continuous renal replacement therapy versus intermittent hemodialysis in intensive care patients: Impact on mortality and renal recovery. Intensive Care Med 2016; 42:1408–1417

20. The GBD 2016 Lifetime Risk of Stroke Collaborators: Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. N Engl J Med 2018; 379:2429–2437

21. Sprung CL, Ricou B, Hartog CS, et al: Changes in end-of-life practices in European intensive care units from 1999 to 2016. JAMA 2019; 322:1692–1704

22. Le Gall JR, Lemeshow S, Saulnier F: A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957–2963

23. Vincent JL, Moreno R, Takala J, et al: The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707–710

24. Teasdale G, Jennett B: Assessment of coma and impaired consciousness. A practical scale. Lancet 1974; 2:81–84

25. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987; 40:373–383

26. Lau B, Cole SR, Gange SJ: Competing risk regression models for epidemiologic data. Am J Epidemiol 2009; 170:244–256

27. Mark NM, Rayner SG, Lee NJ, et al: Global variability in withholding and withdrawal of life-sustaining treatment in the intensive care unit: A systematic review. Intensive Care Med 2015; 41:1572–1585

28. Vesin A, Azoulay E, Ruckly S, et al: Reporting and handling missing values in clinical studies in intensive care units. Intensive Care Med 2013; 39:1396–1404

29. de Mottmollin E, Ruckly S, Schwebel C, et al; OUTCOMEREA Study Group: Pneumonia in acute ischemic stroke patients requiring invasive ventilation: Impact on short and long-term outcomes. J Infect 2019; 79:220–227

30. Holloway RG, Benesch CG, Burgin WS, et al: Prognosis and decision making in severe stroke. JAMA 2005; 294:725–733

31. Sonnerville R, Mazighi M, Bresson D, et al; SPICE investigators: Outcomes of acute stroke patients requiring mechanical ventilation: Study protocol for the SPICE multicenter prospective observational study. Neurocrit Care 2020; 32:624–629

32. Prendergast TJ, Claessens MT, Luce JM: A national survey of end-of-life care for critically ill patients. Am J Respir Crit Care Med 1998; 158:1163–1167

33. Mohammed MA, Mant J, Bentham L, et al: Process of care and mortality of stroke patients with and without a do not resuscitate order in the West Midlands, UK. Int J Qual Health Care 2006; 18:102–106

34. Rabinstein AA, Diringer MN: Withholding care in intracerebral hemorrhage: Realistic compassion or self-fulfilling prophecy? Neurology 2007; 68:1647–1648

35. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology: Guidelines for the management of spontaneous intracerebral hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015; 46:2032–2060

36. Becker KJ, Baxter AB, Cohen WA, et al: Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. Neurology 2001; 56:766–772

37. Frick S, Uehlinger DE, Zuercher Zenklusen RM: Medical futility: Predicting outcome of intensive care unit patients by nurses and doctors—a prospective comparative study. Crit Care Med 2003; 31:456–461

38. Geurts M, de Kort FAS, de Kort PLM, et al: Predictive accuracy of physicians’ estimates of outcome after severe stroke. PLoS One 2017; 12:e0184894

39. Fried TR, Bradley EH, Towle VR: Valuing the outcomes of treatment: Do patients and their caregivers agree? Arch Intern Med 2003; 163:2073–2078
40. Albrecht GL, Devlieger PJ: The disability paradox: High quality of life against all odds. *Soc Sci Med* 1999; 48:977–988
41. Rohaut B, Claassen J: Decision making in perceived devastating brain injury: A call to explore the impact of cognitive biases. *Br J Anaesth* 2018; 120:5–9
42. Sprung CL, Cohen SL, Sjökvist P, et al; Ethicus Study Group: End-of-life practices in European intensive care units: The Ethicus study. *JAMA* 2003; 290:790–797
43. Roger C, Morel J, Molinari N, et al; AzuRea Group: Practices of end-of-life decisions in 66 southern French ICUs 4 years after an official legal framework: A 1-day audit. *Anaesth Crit Care Pain Med* 2015; 34:73–77
44. Kowalski RG, Chang TR, Carhuapoma JR, et al: Withdrawal of technological life support following subarachnoid hemorrhage. *Neurocrit Care* 2013; 19:269–275
45. Qureshi AI, Adil MM, Suri MF: Rate of utilization and determinants of withdrawal of care in acute ischemic stroke treated with thrombolytics in USA. *Med Care* 2013; 51:1094–1100
46. Parry-Jones AR, Paley L, Bray BD, et al; SSNAP Collaborative Group: Care-limiting decisions in acute stroke and association with survival: Analyses of UK national quality register data. *Int J Stroke* 2016; 11:321–331
47. Luengo-Fernandez R, Paul NL, Gray AM, et al; Oxford Vascular Study: Population-based study of disability and institutionalization after transient ischemic attack and stroke: 10-year results of the Oxford vascular study. *Stroke* 2013; 44:2854–2861
48. Hemphill JC 3rd, Bonovich DC, Besmertis L, et al: The ICH score: A simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001; 32:891–897
49. Hunt WE, Hess RM: Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg* 1968; 28:14–20
50. Teasdale GM, Drake CG, Hunt W, et al: A universal subarachnoid hemorrhage scale: Report of a committee of the world federation of neurosurgical societies. *J Neurol Neurosurg Psychiatry* 1988; 51:1457
51. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators: Endovascular thrombectomy after large-vessel ischemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387:1723–1731
52. Albers GW, Marks MP, Kemp S, et al; DEFUSE 3 Investigators: Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; 378:708–718
53. Nogueira RG, Jadhav AP, Haussen DC, et al; DAWN Trial Investigators: Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; 378:11–21