



Universiteit
Leiden
The Netherlands

Long-term mortality among ICU patients with stroke compared with other critically ill patients

Valburg, M.K. van; Termorshuizen, F.; Brinkman, S.; Abdo, W.F.; Bergh, W.M. van den; Horn, J.; ... ; Arbous, M.S.

Citation

Valburg, M. K. van, Termorshuizen, F., Brinkman, S., Abdo, W. F., Bergh, W. M. van den, Horn, J., ... Arbous, M. S. (2020). Long-term mortality among ICU patients with stroke compared with other critically ill patients. *Critical Care Medicine*, 48(10), E876-E883.
doi:10.1097/CCM.0000000000004492

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3182579>

Note: To cite this publication please use the final published version (if applicable).

Long-Term Mortality Among ICU Patients With Stroke Compared With Other Critically Ill Patients

Mariëlle K. van Valburg, MD, BSc¹; Fabian Termorshuizen, PhD^{2,3}; Sylvia Brinkman, PhD^{2,3}; Wilson F. Abdo, MD, PhD⁴; Walter M. van den Bergh, MD, PhD⁵; Janneke Horn, MD, PhD⁶; Walther N. K. A. van Mook, MD, PhD⁷⁻⁹; Bob Siegerink, PhD¹⁰; Arjen J. C. Slooter, MD, PhD^{11,12}; Marieke J. H. Wermer, MD, PhD¹³; Bart F. Geerts, MD, PhD, MSc, MBA¹⁴; M. Sesmu Arbous, MD, PhD^{2,15,16}

Objectives: Assessment of all-cause mortality of intracerebral hemorrhage and ischemic stroke patients admitted to the ICU and comparison to the mortality of other critically ill ICU patients classified into six other diagnostic subgroups and the general Dutch population.

Design: Observational cohort study.

Setting: All ICUs participating in the Dutch National Intensive Care Evaluation database.

Patients: All adult patients admitted to these ICUs between 2010 and 2015; patients were followed until February 2017.

Interventions: None.

Measurements and Main Results: Of all 370,386 included ICU patients, 7,046 (1.9%) were stroke patients, 4,072 with ischemic stroke, and 2,974 with intracerebral hemorrhage. Short-term mortality in ICU-admitted stroke patients was high with 30 days mortality of 31% in ischemic stroke and 42% in intracerebral hemorrhage. In the longer term, the survival curve gradient among ischemic stroke and intracerebral hemorrhage patients stabilized. The gradual alteration of mortality risk after ICU admission was assessed using left-truncation with increasing minimum survival period. ICU-admitted stroke patients who survive the first 30 days after suffering from a stroke had a favorable subsequent survival compared with other diseases necessitating ICU admission such as patients admitted due to sepsis or severe community-acquired pneumonia. After having survived the first 3 months after ICU admission, multivariable Cox regression analyses showed that case-mix adjusted hazard ratios during the follow-up period of up to 3 years were lower in ischemic stroke compared with sepsis (adjusted hazard ratio, 1.21; 95% CI, 1.06–1.36) and severe community-acquired pneumonia (adjusted hazard ratio, 1.57; 95% CI, 1.39–1.77) and in intracerebral hemorrhage patients compared with these groups (adjusted hazard ratio, 1.14; 95% CI, 0.98–1.33 and adjusted hazard ratio, 1.49; 95% CI, 1.28–1.73).

Conclusions: Stroke patients who need intensive care treatment have a high short-term mortality risk, but this alters favorably with increasing duration of survival time after ICU admission in patients with both ischemic stroke and intracerebral hemorrhage, especially compared with other populations of critically ill patients such as sepsis or severe community-acquired pneumonia patients. (*Crit Care Med* 2020; 48:e876–e883)

Key Words: brain ischemia; critical care; intensive care unit; intracranial hemorrhages; mortality; stroke

¹Department of Anesthesiology, University Medical Center Utrecht, Utrecht, The Netherlands.

²National Intensive Care Evaluation Foundation, Amsterdam University Medical Center, Amsterdam, The Netherlands.

³Department of Medical Informatics, Amsterdam University Medical Center, Amsterdam, The Netherlands.

⁴Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands.

⁵Department of Critical Care, University Medical Center Groningen, Groningen, The Netherlands.

⁶Department of Intensive Care, Amsterdam University Medical Center, Amsterdam, The Netherlands.

⁷Department of Intensive Care Medicine, Maastricht University Medical Center, Maastricht, The Netherlands.

⁸Maastricht UMC+ Academy for Postgraduate Training, Maastricht University Medical Center, Maastricht, The Netherlands.

⁹School of Health Professions Education, Maastricht University, Maastricht, The Netherlands.

¹⁰Center for stroke research Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany.

¹¹Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht, The Netherlands.

¹²Brain Center Utrecht University, Utrecht, The Netherlands.

¹³Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands.

¹⁴Department of Anesthesiology, Amsterdam University Medical Center, Amsterdam, The Netherlands.

¹⁵Department of Intensive Care, Leiden University Medical Center, Leiden, The Netherlands.

¹⁶Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands.

Copyright © 2020 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000004492

Stroke is a major global healthcare issue. Despite the declining occurrence rate of stroke and subsequent mortality over time (1), stroke is still the third leading cause of death in the Netherlands (2) and fifth in the United States (3). Furthermore, stroke is a leading cause of functional disability (4).

Stroke-associated cerebral damage can concomitantly cause compromise of other vital organ functions and, consequently, patients may need treatment in the ICU.

With expanding number of treatment and support options, acute stroke care and the need for intensive care will be increasingly intertwined, and an increasing number of stroke patients will be admitted to the ICU in the future (5, 6).

The broad definition of stroke includes ischemic stroke (IS) and intracerebral and subarachnoid hemorrhage (SAH) (7). In practice, SAH differs from acute IS and intracerebral hemorrhage (ICH) with respect to demographics, recuperation, and effect on other organ function due to catecholamine release (8,9). Therefore, this research focuses on patients with IS or ICH admitted to the ICU. Hereafter, we will refer to “stroke” as composite outcome for IS and ICH.

Mortality in patients with IS and ICH admitted to the ICU has been investigated before (10–15), but these studies did not include long-term mortality, were limited to small study populations, and did not compare stroke patients to ICU patients admitted for other diagnoses. Earlier research using the Dutch National Intensive Care Evaluation (NICE) database (16) compared large groups of critically ill patients and assessed case-mix adjusted mortality beyond hospitalization in several diagnostic subgroups (17). However, this study did not include patients with IS and ICH. For other diagnostic subgroups, it is recognized that the sequelae of ICU admission extend beyond hospitalization, but this is still unknown for the subset of stroke patients who need intensive care admission, particularly in the recent era in which treatment modalities for (mainly ischemic) stroke have changed markedly (18–24).

In this contemporary era of innovative treatment modalities for stroke, the aim of this study was to assess all-cause mortality from ICU admission onwards of patients with IS and ICH. Furthermore, we compared this to the mortality of the general population and six predefined diagnostic subgroups (including SAH) of ICU patients and investigated the mortality risk patterns over time after having survived the initial event that led to ICU admission.

MATERIALS AND METHODS

Data Sources

In this cohort study, consecutive adult patients admitted to all ICUs participating in the Dutch NICE database between 2010 and 2015, comprising over 90% (85 ICUs in 2015) of ICUs, were considered eligible and recruited (16). Patients were followed using the national medical insurance claim database Vektis (Vektis Beheer BV, Zeist, The Netherlands). The duration of follow-up ended at death or the last date of observation, as documented in the Vektis database until February 2017. Linkage between the NICE and Vektis database was obtained to

define date of death after ICU admission using a deterministic linkage algorithm (25). Healthcare insurance is compulsory for all Dutch citizens; hence, the Vektis database includes nearly complete coverage of all medical care in The Netherlands. Exclusion criteria were linkage discrepancies between the NICE and Vektis database and not fulfilling the Acute Physiology and Chronic Health Evaluation (APACHE) IV criteria (26).

The mortality rate for stroke patients in this study was compared with the mortality rate of the general Dutch population (GDP). The GDP mortality rate was generated from StatLine (CBS, The Hague, The Netherlands) (2). In order to standardize indirectly, the GDP weighted average death rates were calculated using age and gender distribution with the selected population of stroke patients as standard. Stroke patients were treated according to the most recent national protocol “Ischemic Stroke and Intracranial Hemorrhage” (27) of the Dutch Society for Neurology with involvement of the Dutch Society of Critical Care.

The NICE database is registered according to the Dutch Data Protection Act. The medical ethics committee of the Amsterdam University Medical Center waived informed consent for this study under Dutch national law (Institutional Review Board protocol number W18_049#18.067).

Diagnostic ICU Subgroups

Stroke patients were defined as patients admitted to ICU due to IS or ICH, not including patients with SAH or deep cerebral venous thrombosis. Other patients were classified into predefined diagnostic subgroups according to the APACHE IV classification system: 1) SAH, 2) traumatic brain injury (TBI), 3) sepsis, 4) severe community-acquired pneumonia (sCAP), 5) cardiac surgery, 6) nonsurgical cancer, and 7) other diagnoses. Detailed definitions are shown in **Figure 1**. These groups were chosen in order to compare our stroke study population to populations with other neurologic reasons for ICU admissions (1 and 2), reasons for frequent admissions (5), and with known chronic morbidity and sequelae beyond critical care (3, 4, and 6). All ICU patients except stroke patients were analyzed as a combined group as well.

Statistical Analyses

The primary outcome was defined as all-cause short-term (30 d) and long-term (1 yr) mortality after ICU admission.

First, crude cumulative mortality risks were assessed by Kaplan-Meier survival estimates for patients with (I) IS and (II) ICH, (III) all ICU patients except stroke as a combined group, (IV) the GDP and the above predefined diagnostic ICU subgroups (V-1 to V-6).

Second, to assess the gradual alteration of mortality risk with increasing survival periods and to understand the risk pattern after ICU admission, mortality risk was assessed for patients who survived ICU discharge, 30 days, 3 months, and 1 year. This was done by using left-truncation for these predefined time points. Survival of patients who survived up to these time points was analyzed by repeating the Kaplan-Meier

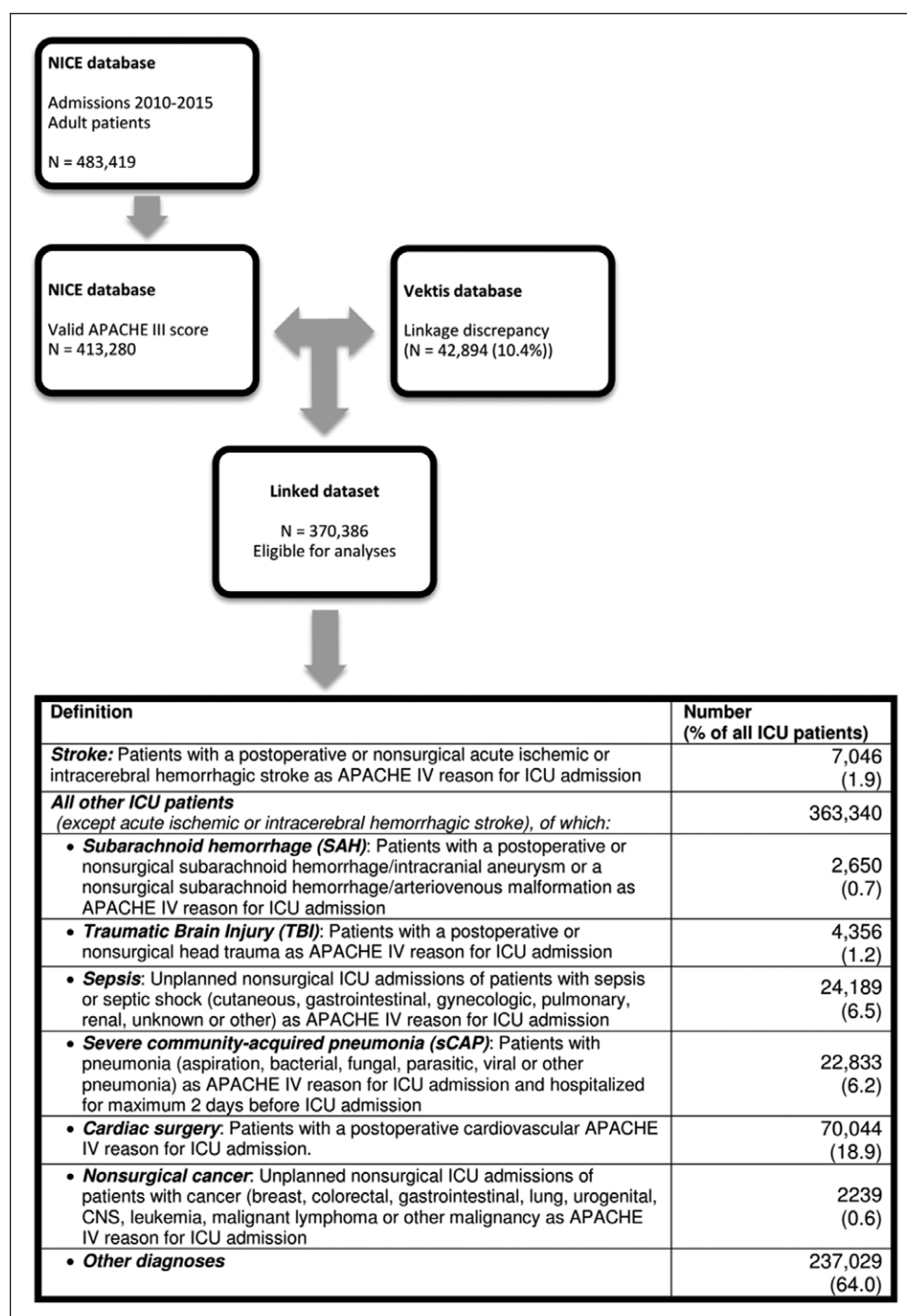


Figure 1. Flowchart of reasons for inclusions and diagnostic subgroup sizes. Out of 483,419 ICU admissions, 370,386 were eligible for analysis, of which 7,046 (1.9%) were stroke patients, 4,072 ischemic stroke, and 2,974 intracerebral hemorrhage patients. APACHE = Acute Physiology and Chronic Health Evaluation, NICE = National Intensive Care Evaluation.

estimates from these points onwards and starting the curve again at 100%.

Third, the differences in mortality between stroke patients and other diagnostic ICU subgroups were analyzed in a multivariable Cox regression model. Case-mix adjusted hazard ratios (HR_{adj}) and corresponding 95% CIs were calculated. The population of

IS and ICH were used as reference groups with the same left-truncations as described above. The HRs were adjusted for age, sex, APACHE III score, and calendar year of ICU admission (2010–2015). Correlation between duration of survival of patients admitted to the same ICU was taken into account by including hospital as a random intercept in the models. Preparation of the data files was done using SPSS, Version 24.0 (IBM Corp., Armonk, NY). The statistical analyses were performed using statistical environment R, Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

During the study period, 483,419 patients were admitted to the participating ICUs. After exclusion of patients not fulfilling the APACHE IV criteria and linkage discrepancies, 370,386 patients were included for analyses. Of the included patients, 7,046 (1.9%) were stroke patients, 4,072 with IS, and 2,974 with ICH (Fig. 1). Baseline characteristics and follow-up data of patients with IS, ICH, all subgroups, and all ICU patients (including stroke) are shown in **Table 1**. **Supplemental Table 1** (Supplemental Digital Content 1, <http://links.lww.com/CCM/F616>) contains baseline characteristics of additional groups, including patients after cardiac surgery, with nonsurgical cancer and the combined group (all ICU patients except stroke).

Demographics were mainly comparable between IS and ICH. Patients with ICH had higher ICU readmission rate and lower Glasgow Coma Scale at admission, while patients with IS had more chronic diagnoses. In 30.9% of patients with ICH, a neurosurgical intervention was performed. In total, 3,366 stroke patients died (48%) during the study period with a median (interquartile range) follow-up of 9.6 months (0.2–23.7 mo).

TABLE 1. Demographics, Length of Stay and Mortality, and Follow-Up in Ischemic Stroke and Intracerebral Hemorrhage Patients and Four of the Six Investigated Other Diagnostic Subgroups (See Supplemental Table 1 [Supplemental Digital Content 1, <http://links.lww.com/CCM/F616>] for Baseline Characteristics of All Groups)

Characteristics	Other Diagnostic Subgroups						All Patients
	Ischemic Stroke	Intracerebral Hemorrhage	Subarachnoid Hemorrhage	Traumatic Brain Injury	Sepsis	Severe Community-Acquired Pneumonia	
<i>n</i> (%)	4,072 (1.1)	2,974 (0.8)	2,650 (0.7)	4,356 (1.2)	24,189 (6.5)	22,833 (6.2)	370,386
Age, mean (sd)	67.5 (13.7)	60.7 (15.1)	58.5 (12.9)	53.3 (20.4)	66.9 (14.2)	66.3 (14.5)	63.9 (15.3)
Sex, men, %	56.5	56.8	35.0	69.9	56.1	59.2	59.5
Daytime admissions (8:00–18:00hr, %)	37.5	33.3	35.3	28.6	35.3	36.5	54.9
One or more chronic diagnoses (%) ^a	18.1	14.6	9.5	8.4	44.3	59.4	33.5
Acute Physiology and Chronic Health Evaluation IV predicted mortality, %, mean (sd)	40 (20)	50 (20)	40 (30)	20 (20)	50 (20)	40 (20)	20 (20)
ICU readmission rate (%)	3.8	6.5	7.6	4.2	6.3	3.3	5.6
Glasgow Coma Scale at admission, mean (sd)	11.1 (4.4)	8.6 (4.7)	10.7 (4.9)	10.0 (4.7)	13.8 (2.6)	13.7 (2.9)	13.7 (3.2)
ICU LOS, d, mean (sd)	2.9 (6.1)	4.6 (8.4)	5.3 (8.0)	5.3 (8.5)	6.2 (10.1)	6.6 (9.4)	3.1 (6.7)
ICU mortality (%)	696 (17)	907 (31)	580 (22)	566 (13)	4,500 (19)	3,347 (15)	29,305 (8)
Of which within 7 d (% of total ICU mortality)	605 (86.9)	808 (89.1)	499 (86.0)	414 (73.1)	3,394 (75.4)	2,096 (62.6)	22,515 (76.8)
Hospital LOS, d, mean (sd)	11.0 (13.2)	13.9 (18.6)	14.3 (15.3)	14.5 (16.6)	20.7 (22.1)	17.3 (23.1)	13.3 (18.1)
Hospital mortality, <i>n</i> (%)	1,172 (29)	1,210 (41)	722 (27)	747 (17)	6,236 (26)	5,193 (23)	44,557 (12)
30-d mortality, <i>n</i> (%)	1,280 (31)	1,263 (42)	748 (28)	776 (18)	6,358 (26)	5,516 (24)	47,796 (13)
3-mo mortality, <i>n</i> (%)	1,476 (36)	1,401 (47)	817 (31)	881 (20)	7,694 (32)	7,026 (31)	60,220 (16)
1-yr mortality, <i>n</i> (%)	1,663 (41)	1,519 (51)	856 (32)	987 (23)	9,394 (39)	8,909 (39)	81,396 (22)
Total amount of deceased patients, <i>n</i> (%)	1,783 (44)	1,583 (53)	879 (33)	1,058 (24)	10,638 (44)	10,480 (46)	99,485 (27)
Follow-up, mo, mean (sd)	13.3 (12.2)	11.1 (12.2)	14.7 (12.3)	17.5 (11.7)	13.9 (12.0)	13.8 (11.8)	17.4 (11.3)
1-yr follow-up, <i>n</i> (%)	2,084 (51.2)	1,249 (42.0)	1,474 (55.6)	2,936 (67.4)	12,684 (52.4)	11,859 (51.9)	245,350 (66.2)
2-yr follow-up, <i>n</i> (%)	1,029 (25.3)	661 (22.2)	803 (30.3)	1,616 (37.1)	6,465 (26.7)	5,706 (25.0)	128,568 (34.7)

LOS = length of stay.

^aChronic diagnoses: chronic obstructive pulmonary disease, respiratory insufficiency, renal insufficiency, cirrhosis, cardiac insufficiency, malignancy, and AIDS/immune deficiency.

Survival Distribution Compared With GDP and Diagnostic ICU Subgroups

The survival of patients with IS was significantly better compared with patients with ICH (log-rank test $p < 0.001$). In both IS and ICH, crude cumulative survival at the end of follow-up was worse compared with the GDP and the combined group of all other ICU patients (Fig. 2). The inset of Figure 2 shows a large decline in survival of stroke patients within the first 10 days after ICU admission with mortality rate of 29%. This is in contrast to the longer term, in which the survival curve gradient among both IS and ICH patients stabilizes.

Survival in cardiac surgery, TBI and SAH patients, remained better than in stroke during the whole follow-up period

(Supplemental Fig. 1, Supplemental Digital Content 2, <http://links.lww.com/CCM/F617>). The crude cumulative survival of sepsis and sCAP, initially better than IS, became worse compared with IS after approximately 18 months. Among all diagnostic subgroups of our ICU populations, patients with ICH and nonsurgical cancer had the lowest cumulative survival with 1-year survival of respectively 49% and 30% (Supplemental Fig. 1a, Supplemental Digital Content 2, <http://links.lww.com/CCM/F617>).

Mortality Risk Patterns Over Time Compared With Diagnostic ICU Subgroups

With an increasing minimum of survival time, using left-truncation, differences in survival curves of patients with IS and ICH

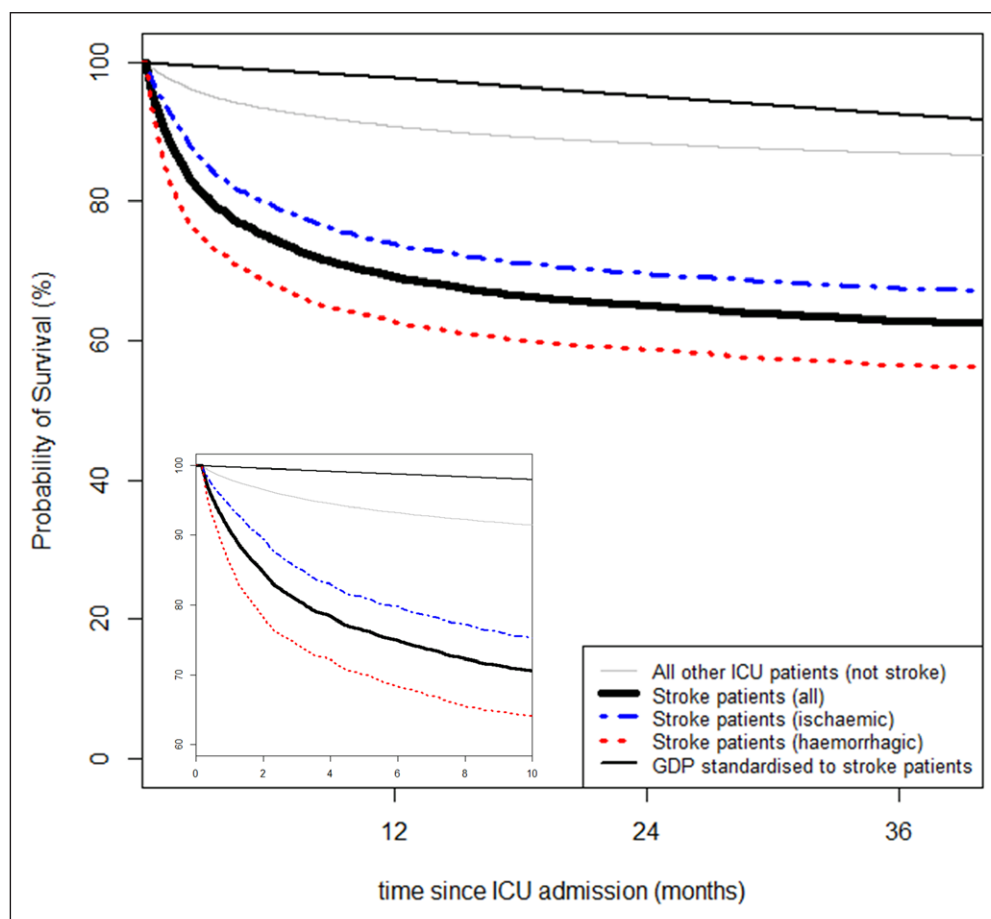


Figure 2. All-cause mortality in patients with (I) ischemic stroke and (II) intracerebral hemorrhage, (III) all other ICU patients as combined separate group and (IV) aggregated general Dutch population (GDP) as expected mortality for the stroke patients in this study population. The inset shows the same data on an expanded y-axis with time in days of the first 10 d after ICU admission.

disappeared, and furthermore, the slope of the Kaplan-Meier survival curves in both IS and ICH became less steep compared with sepsis, sCAP, and nonsurgical cancer. This indicated that the hazard of death (i.e., the slope steepness of a survival curve) in patients with IS and ICH, if they survived the first critical period, gradually decreased over time. This was different in patients admitted due to sepsis or sCAP: after left-truncation of 30 days and longer, the risk of dying due to sepsis, and sCAP surpassed the risk of dying after ICU admission due to IS and ICH (**Supplemental Fig. 2b–e**, Supplemental Digital Content 3, <http://links.lww.com/CCM/F618>).

Alteration of Mortality Risk With Increasing Survival Periods

The hazards of mortality (adjusted for age, sex, APACHE III score, and calendar year of ICU admission) during the maximal follow-up time of 37.1 months of patients with IS (**Supplemental Fig. 2a**, Supplemental Digital Content 3, <http://links.lww.com/CCM/F618>) and ICH (**Supplemental Fig. 2b**, Supplemental Digital Content 3, <http://links.lww.com/CCM/F618>) were compared with the hazards of mortality of all other diagnostic subgroups. **Supplemental Table 2** (Supplemental Digital Content 4, <http://links.lww.com/CCM/F619>) shows mortality rates and APACHE III scores per calendar year of ICU admission in patients with IS, ICH, and all ICU patients except stroke.

The mortality risk in ICH was higher compared with IS without left-truncation (HR_{adj} was significantly higher than 1.00) but this difference disappeared with increasing minimum of survival time (i.e., with applying left-truncation the HR_{adj} became close to and nonsignificantly different from 1.00).

The mortality risk was lower in TBI and cardiac surgery and higher in nonsurgical cancer when compared with either IS or ICH, regardless of whether survival periods were increased, so no alteration of mortality risk occurred compared with IS or ICH.

Among SAH patients, the risk for mortality was lower compared with the mortality risk of patients with ICH, regardless of left-truncation. Compared with IS patients, the hazard was not different in SAH patients when no left-truncation was applied (HR_{adj} , 0.98; 95% CI, 0.90–1.07), but became significantly lower in SAH with increasing minimum of survival time.

HR_{adj} among sepsis and sCAP patients compared with both IS and ICH clearly increased with increasing left-truncation, indicating gradual alteration of mortality risk compared with stroke patients. After having survived the first 30 days after ICU admission, the HR_{adj} 's were no longer significantly lower than 1.00 in both sepsis and sCAP patients compared with stroke patients. After having survived 3 months, the mortality risk was significantly higher in sepsis compared with IS (HR_{adj} , 1.21; 95% CI, 1.06–1.36) and had a tendency to a significant increase compared with ICH (HR_{adj} , 1.14; 95% CI, 0.98–1.33). Among patients with sCAP, the mortality risk after surviving 3 months was significantly higher compared with either IS (HR_{adj} , 1.57; 95% CI, 1.39–1.77) or ICH patients (HR_{adj} , 1.49; 95% CI, 1.28–1.73) (**Supplemental Fig. 2, a and b**, Supplemental Digital Content 3, <http://links.lww.com/CCM/F618>).

DISCUSSION

This national multicenter study has unraveled the survival pattern of patients with IS and ICH admitted to the ICU in a cohort of over 7,000 stroke patients with a follow-up of up to 3 years. We found that stroke patients admitted to the ICU had high short-term mortality, more pronounced in ICH than in IS when compared with other critically ill patients. However,

when a stroke patient survived the first 30 days after ICU admission (69% in IS and 58% in ICH), the prognosis gradually improved. Furthermore, it was shown that mortality risk after surviving 3 months was approaching statistical significance in patients with ICH and significantly lower in IS, compared with both sepsis and sCAP patients. After having survived 1 year, mortality risk in both ICH and IS were significantly lower compared with sepsis and sCAP.

The 1-year mortality rate of 41% in IS and 51% in ICH patients admitted to the ICU found in this study is comparable to earlier studies (10–15, 28–30), although previous literature did not report mortality beyond one year after ICU admission in such a large cohort. Furthermore, the present study did not only compare stroke patients to other neurologic ICU patients (12–14) but also included cardiac surgery patients with low predicted mortality and patients with diagnoses suspected for long-term sequelae and high predicted mortality, such as ICU patients with sepsis, sCAP, and nonsurgical cancer (31). This has led to the observation that long-term mortality in critically ill stroke patients is higher than in TBI or SAH, as shown earlier (12–14) and that the survival patterns of patients with sepsis and sCAP is totally different from stroke patients.

An explanation for this finding may be that stroke can be seen as a one-time event and is mostly failure of a single organ, whereas sepsis is a lengthier and ongoing syndrome with a wide spectrum of underlying chronic conditions and often accompanied with multiple organ involvement. The proportion of patients with one or more chronic diagnosis in all separate diagnostic subgroups in our study (18% in IS and 14% in ICH compared with 44% in sepsis) underlines this explanation. In addition, recent literature has described that patients surviving sepsis acquire new physical disability and cognitive impairment leading to further health deterioration after hospital discharge with an increased hazard of death and therefore implying persistent long-term mortality risk (32–35).

Stroke leads to evident physical and cognitive disability. However, the data in this study show that in ICU-admitted stroke patients it is important to recognize the concept that patients who survive the first 30 days after suffering from a stroke, have a relative favorable subsequent survival compared with other diseases necessitating ICU admission such as patients admitted due to sepsis or sCAP.

The strengths of this study are its large number of admissions from 85 ICUs across the country, the long-term follow-up, and usage of the existing APACHE IV model, which has been validated in the Dutch ICU population (36). Furthermore, we were able to correct for various known determinants in order to confirm our results on mortality risk in stroke patients compared with the other predefined diagnostic ICU subgroups, since risk of mortality is highly correlated to the underlying case-mix of patients (37).

However, some limitations need to be addressed. This was a cohort study with all-cause mortality as outcome variable and therefore not taking reason of death into account, including withdrawal of care and comfort of care transitions. Therefore, the high all-cause mortality in stroke patients might be related

to withdrawal of care in severe cases and selection of patients with less deficits, contributing to the gradual decrease of mortality over time if a patient survived the first period. On the other hand, withdrawal of care does imply clinical deterioration as judged by the members of the healthcare team, so these patients were probably severe stroke patients with an expected high mortality.

Second, our results are limited to the subset of acute stroke patients admitted to the ICU. No extrapolation is possible to IS or ICH patients admitted from the emergency department to the ward or stroke unit due to lack of expected benefit (as judged by the admitting physician) from ICU care on one hand or lack of necessity of ICU care on the other hand. To put our study numbers in perspective, in 2010–2012, approximately 35,000 patients were admitted annually to one of all Dutch hospitals due to suspicion of stroke (20.7–21.1 clinical admissions per 10,000 citizens) (2). More recent, 33,733 stroke patients were registered in 2017 in 71 hospitals within the country. Of patients with IS, 21% received IV thrombolysis and 4.5% underwent intra-arterial thrombectomy (39).

Third, the administrative NICE database creates the possibility to analyze case-mix adjusted long-term mortality far beyond hospitalization in a large and extensive cohort of ICU-admitted stroke patients, but unfortunately does not contain data concerning functional status or posthospital location and therefore this study pertains only to mortality risks of critically ill stroke patients and not to their life's quality or abilities in daily life. Unfortunately, we could not collect data concerning National Institutes of Health Stroke Scale scores (40, 41) or ICH scores (42) via the NICE database. Furthermore, due to linkage discrepancies, 10.4% of the NICE database records were excluded from the study. However, the deterministic linkage algorithm that was used leads to a small number of false-positive links (43), indicating that our linked data set is reliable.

Finally, since we did not possess data concerning vascular territories of stroke or numbers on reperfusion rates or anti-coagulant therapies in respectively IS and ICH, heterogeneity among the study population might have occurred. The unraveled survival pattern in IS and ICH patients admitted to the ICU could be due to homogenous populations with high mortality hazards in short-term and lower in longer term. Another explanation might be that our study group consists of several subgroups with different stroke subtypes within the stroke population with different prognoses and survival patterns.

CONCLUSIONS

Stroke patients who need intensive care treatment have a high short-term mortality risk. However, the mortality risk alters favorably with increasing survival period after ICU admission in patients with both IS and ICH, especially compared with other populations of critically ill patients such as sepsis or sCAP patients. Future research is needed to reveal clinical variables which can identify stroke patients at ICU admission who will survive that first critical period in the ICU. These data can subsequently assist in personalizing critical care and informing patients and their family caregivers about patterns

and probabilities concerning survival and quality of life after ICU admission due to an IS or ICH.

ACKNOWLEDGMENTS

We thank all Dutch ICUs participating in the National Intensive Care Evaluation database for their willingness to continuously collect data for quality improvement and providing these data for research. We thank HandicapNL for financing the Study on Outcome and Prognosis in Hemorrhagic and Ischemic Stroke patients admitted To the Intensive Care project and starting the discussion on the outcomes of stroke after ICU admission and how we can improve their recovery.

This work was performed at Amsterdam University Medical Center, Amsterdam, The Netherlands; Leiden University Medical Center, Leiden, The Netherlands; and University Medical Center Utrecht, Utrecht, The Netherlands.

Bart F. Geerts and M. Sesmu Arbous contributed equally to this article.

Mariëlle K. van Valburg, Bart F. Geerts, and M. Sesmu Arbous designed the study protocol. Mariëlle K. van Valburg, Wilson F. Abdo, Walter M. van den Bergh, Janneke Horn, Walther N. K. A. van Mook, Bob Siegerink, Arjen J. C. Slooter, Marieke J. H. Wermer, Bart F. Geerts, and M. Sesmu Arbous created the study project. Fabian Termorshuizen and Sylvia Brinkman analyzed the data and performed the statistical analyses. Mariëlle K. van Valburg and Fabian Termorshuizen wrote the draft, and all coauthors critically revised the article and approved the final version for publication.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjournal>).

The Study on Outcome and Prognosis in Hemorrhagic and Ischemic Stroke patients admitted To the Intensive Care (SOPHISTIC) project, and the resulting research has received funding from HandicapNL (former Revalidatiefonds) under project number R2015057 for financing the linkage of the National Intensive Care Evaluation database to the Vektis national insurance claim database.

Fabian Termorshuizen's institution received funding from Stichting National Intensive Care Evaluation (NICE) Foundation (ongoing financial support of all research projects with registered data of the NICE database), and he received funding from Mental Health Care Institute Rivierduinen, Leiden, The Netherlands (employment as a data scientist). Fabian Termorshuizen and Bart F. Geerts disclosed that the Study on Outcome and Prognosis in Hemorrhagic and Ischemic Stroke (SOPHISTIC) patients admitted To the Intensive Care project and the following research leading to these results had received funding from HandicapNL (former Revalidatiefonds) under project number R2015057 for financing the linkage of the NICE database to the Vektis national insurance claim database. Sylvia Brinkman disclosed that she is a NICE researcher. The remaining authors have disclosed that they do not have any potential conflicts of interest.

The National Intensive Care Evaluation database is registered according to the Dutch Data Protection Act. The medical ethics committee of the Amsterdam University Medical Center waived informed consent for this study under Dutch national law (Institutional Review Board protocol number W18_049#18.067).

The Study on Outcome and Prognosis in Hemorrhagic and Ischemic Stroke patients admitted To the Intensive Care (SOPHISTIC) project was registered in the Dutch Trial Registry (<https://www.trialregister.nl/>) as NTR7438.

For information regarding this article, E-mail: b.f.geerts@amsterdamumc.nl

REFERENCES

1. Rothwell PM, Coull AJ, Giles MF, et al; Oxford Vascular Study: Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* 2004; 363:1925–1933
2. StatLine Database of the Dutch Governmental Institution Statistics Netherlands (Centraal Bureau voor de Statistiek (CBS)). Available at: <http://statline.cbs.nl/Statweb/>. Accessed November 1, 2018
3. Kochanek KD, Murphy S, Xu J, et al: Mortality in the United States, 2016. *NCHS Data Brief* 2017;1–8
4. Benjamin EJ, Blaha MJ, Chiuve SE, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics-2017 update: A report from the American Heart Association. *Circulation* 2017; 135:e146–e603
5. Kirkman MA, Citerio G, Smith M: The intensive care management of acute ischemic stroke: An overview. *Intensive Care Med* 2014; 40:640–653
6. Llinas RH: Ischemic stroke and ICU care. *Semin Neurol* 2008; 28:645–656
7. Sacco RL, Kasner SE, Broderick JP, et al; American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Council on Nutrition, Physical Activity and Metabolism: An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:2064–2089
8. Nieuwkamp DJ, de Wilde A, Wermer MJ, et al: Long-term outcome after aneurysmal subarachnoid hemorrhage-risks of vascular events, death from cancer and all-cause death. *J Neurol* 2014; 261:309–315
9. Pinnamaneni S, Aronow WS, Frishman WH: Neurocardiac injury after cerebral and subarachnoid hemorrhages. *Cardiol Rev* 2017; 25:89–95
10. Navarrete-Navarro P, Rivera-Fernández R, López-Mutuberria MT, et al: Outcome prediction in terms of functional disability and mortality at 1 year among ICU-admitted severe stroke patients: A prospective epidemiological study in the south of the European Union (Evascan Project, Andalusia, Spain). *Intensive Care Med* 2003; 29:1237–1244
11. Handschu R, Haslbeck M, Hartmann A, et al: Mortality prediction in critical care for acute stroke: Severity of illness-score or coma-scale? *J Neurol* 2005; 252:1249–1254
12. Broessner G, Helbok R, Lackner P, et al: Survival and long-term functional outcome in 1,155 consecutive neurocritical care patients. *Crit Care Med* 2007; 35:2025–2030
13. Kipphuth IC, Schellinger PD, Köhrmann M, et al: Predictors for good functional outcome after neurocritical care. *Crit Care* 2010; 14:R136
14. Pelosi P, Ferguson ND, Frutos-Vivar F, et al; Ventila Study Group: Management and outcome of mechanically ventilated neurologic patients. *Crit Care Med* 2011; 39:1482–1492
15. Alonso A, Ebert AD, Kern R, et al: Outcome predictors of acute stroke patients in need of intensive care treatment. *Cerebrovasc Dis* 2015; 40:10–17
16. Dutch National Intensive Care Evaluation (NICE) Foundation. Available at: <http://www.stichting-nice.nl>. Accessed November 1, 2018
17. Brinkman S, de Jonge E, Abu-Hanna A, et al: Mortality after hospital discharge in ICU patients. *Crit Care Med* 2013; 41:1229–1236
18. Broderick JP, Palesch YY, Demchuk AM, et al; Interventional Management of Stroke (IMS) III Investigators: Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; 368:893–903
19. Ciccone A, Valvassori L, Nichelatti M, et al; SYNTHESIS Expansion Investigators: Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013; 368:904–913
20. Kidwell CS, Jahan R, Gornbein J, et al; MR RESCUE Investigators: A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013; 368:914–923
21. Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators: A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015; 372:11–20
22. Goyal M, Demchuk AM, Menon BK, et al; ESCAPE Trial Investigators: Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015; 372:1019–1030
23. Prabhakaran S, Ruff I, Bernstein RA: Acute stroke intervention: A systematic review. *JAMA* 2015; 313:1451–1462
24. Goyal M, Menon BK, van Zwam WH, et al; HERMES collaborators: Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials. *Lancet* 2016; 387:1723–1731

25. Roos LL, Wajda A: Record linkage strategies. Part I: Estimating information and evaluating approaches. *Methods Inf Med* 1991; 30:117–123
26. Zimmerman JE, Kramer AA, McNair DS, et al: Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; 34:1297–1310
27. Nederlandse Vereniging voor Neurologie (Dutch Society for Neurology): Specialisten KVMS Richtlijn herseninfarct en hersenbloeding. Utrecht, The Netherlands, Nederlandse Vereniging voor Neurologie (Dutch Society for Neurology), 2017, pp 1–318. Available at: https://nvc.nl/sites/nvic.nl/files/Richtlijnen_aanmaken/Richtlijnherseinfarct_en_hersenbloeding.pdf. Accessed September 10, 2019
28. Jeng JS, Huang SJ, Tang SC, et al: Predictors of survival and functional outcome in acute stroke patients admitted to the stroke intensive care unit. *J Neurol Sci* 2008; 270:60–66
29. Riachy M, Sfeir F, Sleilaty G, et al: Prediction of the survival and functional ability of severe stroke patients after ICU therapeutic intervention. *BMC Neurol* 2008; 8:24
30. van Valburg MK, Arbous MS, Georgieva M, et al: Clinical predictors of survival and functional outcome of stroke patients admitted to critical care. *Crit Care Med* 2018; 46:1085–1092
31. de Vries VA, Müller MCA, Sesmu Arbous M, et al; HEMA-ICU Study Group: Time trend analysis of long term outcome of patients with haematological malignancies admitted at Dutch intensive care units. *Br J Haematol* 2018; 181:68–76
32. Linder A, Lee T, Fisher J, et al: Short-term organ dysfunction is associated with long-term (10-yr) mortality of septic shock. *Crit Care Med* 2016; 44:e728–e736
33. Schuler A, Wulf DA, Lu Y, et al: The impact of acute organ dysfunction on long-term survival in sepsis. *Crit Care Med* 2018; 46:843–849
34. Shankar-Hari M, Rubenfeld GD: Understanding long-term outcomes following sepsis: Implications and challenges. *Curr Infect Dis Rep* 2016; 18:37
35. Prescott HC, Angus DC: Enhancing recovery from sepsis: A review. *JAMA* 2018; 319:62–75
36. Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, et al: External validation of Acute Physiology and Chronic Health Evaluation IV in Dutch intensive care units and comparison with Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II. *J Crit Care* 2011; 26:105.e11–e18
37. Brinkman S, Bakhshi-Raiez F, Abu-Hanna A, et al: Determinants of mortality after hospital discharge in ICU patients: Literature review and Dutch cohort study. *Crit Care Med* 2013; 41:1237–1251
38. Dutch Institute for Clinical Auditing (DICA): Dutch Acute Stroke Audit (DASA) As Part of the Dutch Institute for Clinical Auditing (DICA). 2017. Available at: <https://dica.nl/jaarrapportage-2017/dasa>. Accessed February 1, 2019
39. Lyden P, Brott T, Tilley B, et al: Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* 1994; 25:2220–2226
40. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333:1581–1587
41. Besmertis C, Manley GT, Johnston SC: The ICH score. *Stroke* 2001; 32:891–897
42. Tromp M, Ravelli AC, Bonsel GJ, et al: Results from simulated data sets: Probabilistic record linkage outperforms deterministic record linkage. *J Clin Epidemiol* 2011; 64:565–572