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Stachulski, F.; Siegerink, B.; Bosel, J.

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Dying in the Neurointensive Care Unit After Withdrawal of Life-Sustaining Therapy: Associations of Advance Directives and Health-Care Proxies With Timing and Treatment Intensity

Frank Stachulski, MD[1], Bob Siegerink, PhD[2], and Julian Bösel, MD[3,4]

Abstract

Background and Purpose: Critically ill patients require a careful approach for prognosis and decision-making. The German health legislation aims to strengthen the role of advance directives (ADs) and health-care proxies (HCPs). Their impact within a dedicated neurocritical care setting is unknown. This study aimed to assess the practice of withdrawal or withholding of life-sustaining therapy (WOLST) in a German neurointensive care unit (NICU) focusing on whether AD or HCP is associated with timing and treatment intensity. **Methods:** Data on patients who died after WOLST at a dedicated NICU of a German university hospital, from 2010 to 2013, were retrospectively analyzed. **Results:** Of 400 deceased patients, 310 (77.5%) died after initiation of WOLST. Among them, 68 (21.9%) were identified to have AD or HCP or both (AD + HCP). WOLST patients with AD, HCP, or AD + HCP were older than those without (median age: 77 vs 72 years, $P < .001$) but did not show any other distinct baseline features. There was no difference in the specific neurocritical care measures between the groups. Poisson regression analysis showed no significant difference in the probability of time-dependent WOLST initiation between those with and without AD/HCP, after adjusting for age and sex (adjusted incidence rate ratio, 1.10; 95% confidence interval, 0.94-1.28; $P = .244$). **Conclusions:** In this single-center study of mainly cerebrovascular NICU patients, AD or HCP was neither associated with an earlier WOLST nor associated with a difference in treatment intensity before WOLST. Further prospective studies should assess the emerging concept of advance care planning in neurocritical care.

Keywords

neurocritical care, withdrawal of life-sustaining therapy, advance care planning, end-of-life, advance directive

Introduction

About 30% to 85% of all critically ill patients admitted to general or mixed intensive care units (ICUs) die after a decision to withdraw or withhold life-sustaining therapy (WOLST).[1-4] Studies on end-of-life (EOL) practices have yielded an increasing number of recommendations and guidelines regarding consent.[5-7] However, there are limited data regarding patients in neurointensive care units (NICUs), although these are urgently needed to improve decision-making and approaches to palliative care, as well as to guide patients' relatives.[8,9] Neurointensive care unit patients are different from other intensive care patients with regard to epidemiology, time trajectories of onset and course, prognostic models, and systemic complications.[10,11]

The concept of anticipatory decision-making, particularly advance directives (ADs), has gained increasing public attention in high-income countries. In 2009, AD was settled as a binding directive for health-care providers within the German civil law code. Additionally, the position of the appointed health-care proxy (HCP), issued by the patient while still competent, was strengthened. Most German AD templates now include a designated HCP. The scope of AD templates is not limited to terminal disease, but to be valid, the content has to be specific to therapeutic measures.

[1] Department of Neurology, German Allied Forces Hospital Berlin, Germany
[2] Center for Stroke Research (CSB), Charité Universitätsmedizin Berlin, Germany
[3] Department of Neurology, Kassel General Hospital, Kassel, Germany
[4] Department of Neurology, University Hospital Heidelberg, Germany

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Corresponding Author:
Julian Bösel, Department of Neurology, Klinikum Kassel, Mönchebergstr. 41-43, 34125 Kassel, Germany.
Email: julian.boesel@klinikum-kassel.de

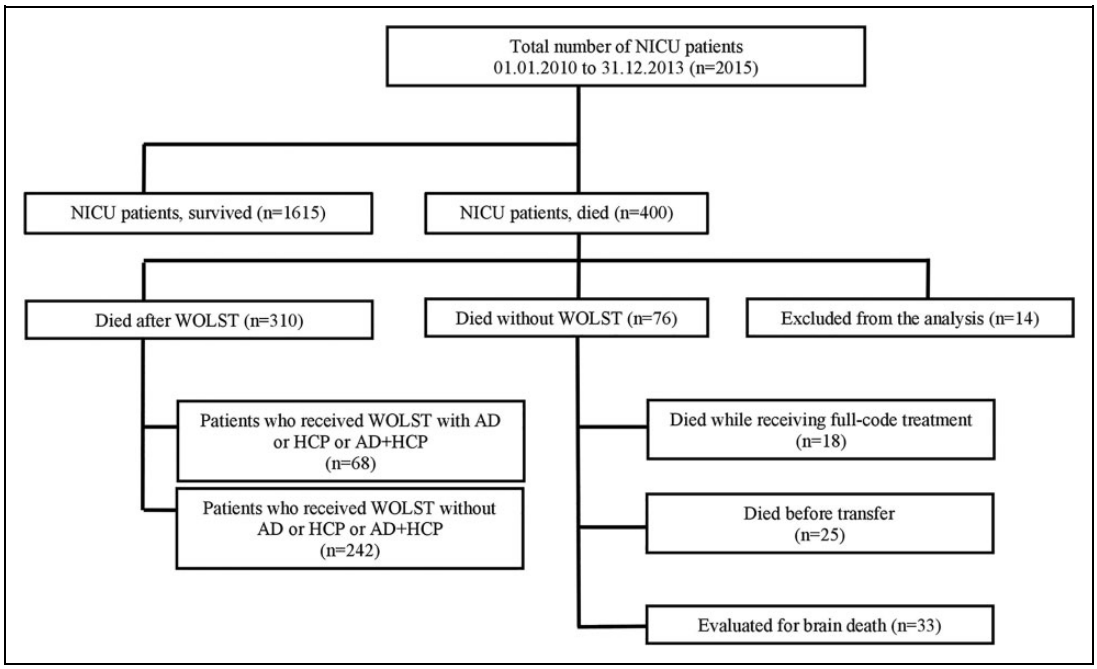

Figure 1. Flowchart of outcomes among NICU patients and selection of study cohorts. AD indicates advance directive; HCP, health-care proxy; NICU, neurointensive care unit; WOLST, withholding/withdrawal of life-sustaining therapy.

Acute cerebrovascular neurological diseases, such as severe acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH), pose a particular challenge for decision-making. These rapidly evolving conditions are frequently associated with uncertain and variable prognoses, as well as potentially devastating functional outcomes. Furthermore, patients with acute brain injuries are often unable to provide consent due to declined consciousness, sedation, or neurocognitive dysfunction. A decision for WOLST may, therefore, be associated with inadequate timing and over- or undertreatment. The impact of anticipatory decision-making instruments (such as ADs or HCPs) or a combination thereof has not been studied thoroughly in the field of neurocritical care.

This study aimed to investigate the practice of WOLST in a German NICU environment under the new legislation. The focus was to determine whether the presence of an AD, HCP, or both is associated with a time difference in the initiation of WOLST and influences the treatment intensity of neurocritical care provided before WOLST.

Methods

Study Design and Setting

This study analyzed single-center data collected at the dedicated NICU of the Department of Neurology at Heidelberg University Hospital, Germany. This 12-bed NICU run entirely by neurointensivists, focuses on cerebrovascular patients, and is part of a comprehensive stroke center that provides a neurosurgical and neuroradiological service 24 hours a day, 7 days a week. During the study period, no standard operating procedure for consent regarding EOL decision-making was in place. There was also no early do-not-resuscitate order policy in place at that time. Both procedures were performed at the discretion of the care team in charge and aimed for consent within the team and with the health-care surrogates. The study protocol was approved by the local Medical Ethics Committee of the University of Heidelberg (Ethikkommission Med. Fakultät Heidelberg S 006-2016). The need for informed consent was waived since only routinely collected clinical data were analyzed.

Data Collection

We extracted data for all patients treated at the NICU between January 1, 2010, and December 31, 2013, who died before discharge from the clinical data system. The patients were differentiated according to whether they died after WOLST or without WOLST during NICU treatment, based on information contained in their complete electronic patient file and digitalized handwritten NICU chart (Figure 1). Only patients who died after WOLST were included in our analysis of AD/HCP status. We did not define a specific minimum time window for the length of stay in the NICU. However, patients who were solely transferred to the NICU for defined procedures (eg, intubation) and those with missing data were excluded from the analysis. All accessible files were reviewed for the presence of an AD or HCP or AD + HCP. The variables assessed were baseline demographic and clinical characteristics (such as sex, diagnosis at admission, age, prior setting of residence, premorbid modified Rankin scale [mRS] score, and National Institutes of Health Stroke Scale [NIHSS] score), prespecified relevant comorbidities, features of NICU treatment, and complications observed during NICU treatment (as specified in the hospital

discharge letter and according to the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems*, but independent of the stage of disease). Early or controlled cancer was defined as cancer with potentially curative treatment, while metastatic cancer or cancer with palliative treatment was referred to as advanced cancer. Neurodegenerative conditions taken into account were motor neuron diseases and diseases of the basal ganglia, such as Parkinson's disease.

In this study, WOLST was defined as either the withdrawal or withholding of life support, as both concepts share ethical, legal, and medical implications in Germany. Withdrawal or withholding of life-sustaining therapy was not further differentiated as to how exactly it was carried out (eg, compassionate extubation, ventilation disconnection, treatment de-escalation, or limitation of organ replacement therapy). All decisions regarding WOLST were made at a clinical conference with an attending board-certified neurologist and/or intensivist, according to German regulations.

Statistical Analysis

All results are expressed as frequen and percentage or mean with standard deviation for continuous variables and median with interquartile range (IQRs) for continuous non-parametric variables. Differences between groups were assessed using Student *t* test, Mann-Whitney *U* test, and χ^2 test, as appropriate. Hazard ratios and incidence rate ratios with their corresponding confidence intervals (CIs) were obtained via Cox proportional hazards regression and Poisson regression, as measures of relative risk in a time-to-event analysis. Records with missing values were excluded from the analysis. A *P* value of less than .05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 22.0 (IBM Corp, Armonk, New York) and Stata version 14 (StataCorp LLC, College Station, Texas).

Results

A total of 2015 patients were admitted to the NICU during the 3-year study period, and 400 (overall mortality rate, 19.9%) of them died in the hospital. Hidden NICU mortality due to transfer before death was identified to account for only 2.9% of all deaths (Figure 1). Among these 400 NICU patients, 310 (77.5%) died after consenting to WOLST. The median age of these patients was 74 years, 42.3% were female, and the diagnoses at admission were mainly cerebrovascular conditions (84.2%); specifically, 39.4% of all patients were diagnosed with AIS, 36.5% with ICH, and 5.8% with SAH. The patients were mainly admitted via the local emergency department (50.3%), while 49.3% were transferred as inpatients or referred from regional primary centers. The majority of patients were previously independent, as indicated by premorbid mRS scores of 0 to 1 (52.6%) and admitted from their private homes (91.3%). The most prevalent comorbidities were prior stroke (21.0%) and cancer (20.9%). Regarding the NICU course, 84.5% of all patients received mechanical ventilation and 28.7% of patients with cerebrovascular disorders underwent neurosurgery. Among patients with AIS and SAH, 50.7% underwent invasive neuroradiological therapy. Except for sepsis (10.0%), medical complications were rare.

Univariate analysis revealed significant differences in the proportions of NICU patients who died after or without WOLST (Table 1). Compared with patients who died without WOLST, patients with WOLST were older ($P < .001$), had an AD or HCP or both ($P = .009$), spent more days in the NICU (3 vs 2 days, $P = .048$), and were more often diagnosed with a cerebrovascular disorder on admission ($P < .001$). The groups also differed regarding the distribution of major complications during NICU treatment and features of disease severity and treatment intensity (Table 1). Compared with death without WOLST, death after WOLST was independently associated with age (odds ratio, 1.04 per year; 95% CI, 1.03-1.07) and cerebrovascular disorder as a diagnosis at admission (adjusted odds ratio [aOR], 2.86; 95% CI, 1.59-5.10) as well as comorbid advanced cancer (aOR, 3.31; 95% CI, 1.13-14.16) after adjusting for covariates (age and sex). Advance directive or HCP or both was associated with double odds of WOLST (aOR, 2.06; 95% CI, 0.93–5.19).

Sixty-eight (21.9%) of the 310 patients who died after WOLST had an AD (n = 34), HCP (n = 21), or both (n = 13). Apart from age (77 vs 72 years, $P < .001$) and proportion of cases of sepsis (2.9% vs 12.0%, $P = .036$), there were no significant differences between the 2 groups regarding features of comorbidity or treatment intensity (Table 2). The time-dependent initiation of WOLST was assessed and depicted for the groups with and without AD/HCP using the Kaplan-Meier method (Figure 2). We compared the 2 groups using the median time from admission to WOLST initiation, due to the skewness of data. In this regard, there was a significant difference between the AD/HCP group (1 day; IQR, 3) and the group without AD/HCP (2 days; IQR, 5, $P = .02$). However, further multivariate Cox and Poisson regression analyses indicated that the rate of WOLST initiation was only slightly increased in the group with AD/HCP (hazard ratio, 1.26; 95% CI, 0.96-1.65; $P = .095$; incidence rate ratio, 1.54; 95% CI, 1.33-1.78; $P < .001$). When this was adjusted for age and sex, a small difference disappeared, suggesting that the initial association, if any, could be attributed to differences in these key patient characteristics between the groups with and without AD/HCP (Table 3). Additional inclusion of other covariables (comorbidities and prior setting of residence) did not alter this result.

Discussion

In this single-center analysis of 2015 NICU patients, 310 of 400 patients died after consented WOLST. This was not initiated earlier in patients with AD/HCP than in those without. Furthermore, there was no difference in the intensity of treatment before WOLST between patients with and without AD/HCP.

So far, only a few studies have focused on the impact of ADs on intensive care treatment, including EOL decisions.[12]

Table 1. Deceased NICU Patients Features According to WOLST Status.[a]

	Deceased NICU Patients After WOLST (n = 310)	Deceased NICU Patients Without WOLST (n = 76)	*P* Value
Baseline clinical data			
Age (years)	74 (14)	68 (21.8)	<.001
Female	131 (42.3%)	32 (42.1%)	.999
Premorbid mRS	1 (3)	1 (3)	.530
AD/HCP	68 (21.9%)	7 (9.2%)	.009
NICU days	3 (4)	2 (4.25)	.048
Diagnosis on admission			
CVD	261 (84.2%)	47 (61.8%)	<.001
Non-CVD	49 (15.8%)	29 (38.2%)	
AIS, NIHSS	23 (18.75)	19 (22.75)	.341
ICH, NIHSS	33 (15)	37 (7)	.007
sICH, volume >25 mL	72 (81.8%)	7 (77.8%)	.671
ICH with IVH	82 (72.6%)	12 (75%)	.999
SAH, WFNS grade	4 (1.75)	4 (3)	.785
Complicating diagnosis during ICU treatment			
Cardiac arrest, CPR	17 (5.5%)	18 (23.8%)	<.001
Sepsis	31 (10%)	20 (26.3%)	<.001
Myocardial infarction	11 (3.5%)	10 (13.1%)	.003
Prior comorbidity			
Early or controlled cancer	28 (9%)	11 (14.5%)	.198
Advanced cancer	37 (11.9%)	3 (3.9%)	.055
Prior stroke or CVD	65 (21%)	12 (15.8%)	.341
Dementia and/or neurodegenerative disorder	35 (11.3%)	8 (10.5%)	.999
CHF	33 (10.6%)	13 (17.1%)	.164
CRF	34 (11%)	7 (9.2%)	.835
Intervention prior to WOLST decision			
Neurosurgical intervention (in patients with CVD only)	82 (31.4%)	14 (29.8%)	.866
Neuroradiological intervention (in patients with AIS/SAH only)	71 (50.7%)	11 (39.3%)	.305
New renal replacement therapy	5 (1.6%)	5 (6.6%)	.028
Vasopressors (>1)	49 (15.8%)	12 (15.8%)	.999
Mechanical ventilation	262 (84.5%)	70 (92.1%)	.098
Days on ventilator	2 (5)	2.5 (4.75)	.266
Tracheostomy	21 (6.8%)	7 (9.2%)	.461

Abbreviations: AD, advance directive; AIS, acute ischemic stroke; CHF, chronic heart failure; CPR, cardiopulmonary resuscitation; CRF, chronic renal failure; CVD, cerebrovascular disease; ICH, intracerebral hemorrhage; ICU, intensive care unit; IVH, intraventricular hemorrhage; HCP, health-care proxy; NICU, neurointensive care unit; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SAH, Subarachnoid hemorrhage; sICH, supratentorial intracerebral hemorrhage; WFNS, World Federation of Neurosurgical Societies; WOLST, withdrawal/withholding of life sustaining therapy.
[a]Results are presented as median and interquartile range (IQR = Q3-Q1) or number of patients and proportions.

Data from dedicated oncologic ICUs revealed no differences in treatment intensity and in-hospital mortality between cancer patients with and without ADs, which is in line with our results.[13,14] Hartog and colleagues found that ADs had no impact on length of stay in the ICU and therapy-limiting decisions but an increased number of do-not-resuscitate orders and less frequent cardiopulmonary resuscitation in a mixed ICU setting with only a few neurocritical care patients.[15] A Canadian multicenter prospective study of ICU patients older than 80 years concluded that ADs had no significant impact on time from admission to death and life-sustaining treatment.[16]

These results are in agreement with ours; however, their comparability is limited due to the distinct clinical characteristics of predominantly cerebrovascular patients with AIS, ICH, and SAH in our cohort. Neurointensivists are regularly faced with situations of EOL and treatment limitation very early after patient admission, not only due to disease severity or multi-organ failure but in view of the often expectedly poor functional outcome.[17] Contrary to the results obtained in mixed ICU settings, only 5.5% of all patients who received WOLST in this cohort had prior cardiopulmonary resuscitation, only 10% were diagnosed with sepsis, and only 1.6% received any form of new renal replacement therapy after admission. Neurointensive care unit patients instead comprise a challenging group with respect to time trajectories of illness, sudden loss of the ability to provide informed consent, and a demand for early aggressive treatment decisions. The premature withdrawal or withholding of treatment efforts inflicted by an ambiguous AD or a struggling HCP could potentially create a self-fulfilling prophecy for a devastating outcome. This is challenging for neurointensivists in particular.[18,19] Factors that contribute to

Table 2. Characteristics of WOLST Patients According to AD/HCP Status.[a]

	WOLST Patients With AD/HCP (n = 68)	WOLST Patients Without AD/HCP (n = 242)	*P* Value
Baseline clinical data			
Age (years)	77 (7.5)	72 (16.5)	<.001
Age >70 years	53 (77.9%)	137 (56.6%)	.134
Female	33 (48.5%)	146 (60.3%)	.417
Premorbid mRS	2 (3)	1 (3)	.092
AD/HCP	33 (48.5%)	146 (60.3%)	.417
NICU days	2 (3)	1 (3)	.092
Prior setting of residence			
Private home	63 (92.6%)	220 (90.9%)	.999
Nursing facility	5 (7.4%)	17 (7.0%)	.999
Diagnosis on admission			
CVD	58 (85.3%)	203 (83.9%)	.852
Non-CVD	10 (14.7%)	39 (16.1%)	
AIS, NIHSS	31 (19)	22 (17.5)	.127
AIS, NIHSS > 20	13 (57.4%)	53 (53%)	.239
ICH, NIHSS	32 (15.5)	33 (15)	.913
sICH, volume >25 mL	22 (81.5%)	50 (81.9%)	.999
ICH with IVH	23 (74.3%)	59 (71.9%)	.999
SAH, WFNS grade	3 (2)	4 (1.2)	.767
Complicating diagnosis during ICU treatment			
Cardiac arrest, CPR	5 (7.4%)	12 (5.0%)	.544
Sepsis	2 (2.9%)	29 (12.0%)	.036
Myocardial infarction	3 (4.4%)	8 (3.3%)	.711
Prior comorbidity			
Early or controlled cancer	4 (5.9%)	24 (9.9%)	.472
Advanced cancer	10 (14.7%)	27 (11.2%)	.405
Prior stroke or CVD	16 (25.0%)	48 (19.8%)	.399
Dementia and/or neurodegenerative disorder	10 (14.7%)	25 (10.3%)	.384
CHF	6 (8.8%)	27 (11.2%)	.662
CRF	9 (13.2%)	25 (10.3%)	.512
Intervention prior to WOLST decision			
Neurosurgical intervention (in patients with CVD only)	14 (24.1%)	68 (33.5%)	.201
Neuroradiological intervention (in patients with AIS/SAH only)	10 (41.7%)	61 (52.6%)	.375
New renal replacement therapy	1 (1.4%)	4 (1.6%)	.999
Vasopressors (>1)	6 (8.8%)	43 (17.8%)	.090
Mechanical ventilation	54 (79.4%)	208 (75.9%)	.188
Days on ventilator	1 (3)	2 (5)	.266
Tracheostomy	3 (4.4%)	18 (7.4%)	.584
Patient's surrogate consenting to WOLST			
Legal guardian	4 (5.9%)	19 (7.8%)	.794
Partner or relative	64 (94.1%)	229 (94.6%)	.771

Abbreviations: AD, advance directive; AIS, acute ischemic stroke; CHF, chronic heart failure; CPR, cardiopulmonary resuscitation; CRF, chronic renal failure; CVD, cerebrovascular disease; ICH, intracerebral hemorrhage; ICU, intensive care unit; IVH, intraventricular hemorrhage; HCP, health-care proxy; NICU, neurointensive care unit; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SAH, subarachnoid hemorrhage; sICH, supratentorial intracerebral hemorrhage; WFNS, World Federation of Neurosurgical Societies; WOLST, withdrawal/withholding of life sustaining therapy.
[a]Results are presented as median and interquartile range (IQR = Q3-Q1) or number of patients and proportions.

self-fulfilling prophecies lie within the individual physician (eg, level of experience, communication skills, training in EOL discussions, personal bias, and working field of the treating physician) and the knowledge and careful interpretation of the underlying data for determining the prognosis.[20,21] These could potentially lead to a decreased treatment intensity even before WOLST is discussed with the patient's surrogate. However, we did not detect relevant treatment neglect in the group with AD/HCPs in our cohort, which is reassuring.

As far as timing is concerned, it is certainly debatable whether a shorter time to WOLST decision is desirable at all. This may mean a premature deprivation of perspective before the clinical course and prognosis become clear enough. Conversely, it may reduce nonbeneficial, prolonged care against the patient's will. We consider the latter the more relevant situation. Although we observed a trend to reduction of time to WOLST, this did not prevail in further statistical analysis. This lack of association with timing of WOLST may have

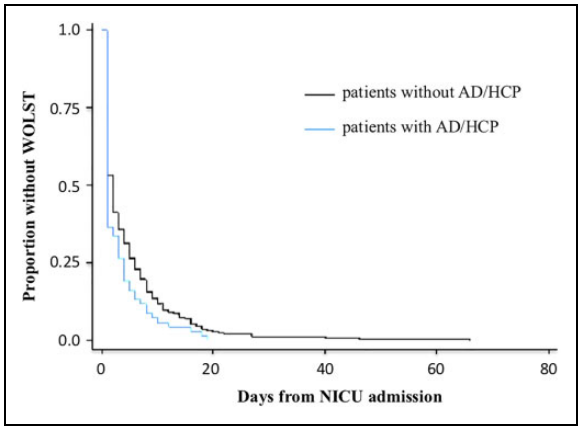

Figure 2. Kaplan-Meier for time from NICU admission to WOLST of deceased patients. The dark curve represents patients without AD/HCP, the light curve represents patients with AD/HCP. AD indicates advance directive; HCP, health-care proxy; NICU, neurointensive care unit; WOLST, withholding/withdrawal of life-sustaining therapy.

several reasons. First, there is little evidence from clinical studies that ADs affect surrogate satisfaction, decrease health-care costs, enhance decision-making in intensive care, or improve physicians' knowledge about patient's preferences.[22-24] Second, the applicability of ADs in the acute NICU setting may be limited,[25] as common German AD templates refer to conditions, such as chronic disorders of consciousness, advanced dementia, terminal illness, and imminent death, which are rarely present or at least cannot be confirmed with certainty in early neurocritical care. Even if ADs are applicable, a delay in their fulfilment may be caused by suboptimal communication, such as disagreement between the intensive care team and the surrogate, hospital logistics, family wishes, or paternalistic values among physicians.[25] Third, research on NICU prognosis has focused on mortality rather than quality of life. Judgment of the latter varies considerably between physicians and patients, that is, they tend to disagree as to which outcome is considered acceptable.[26] For example, the DEcompressive Surgery for the Treatment of malignant InfarctioN of the middle cerebral arterY II (DESTINY II) investigators detected a surprisingly high rate of retrospective consent to decompressive hemicraniectomy after large hemispheric infarction among patients and their relatives.[27] By contrast, a recent survey by the IGNITE (Initiative of German NeuroIntensive Trial Engagement) study group revealed that only 24.5% of stroke physicians and patients considered an mRS score of 4 (not able to walk without assistance) after stroke as an "acceptable" outcome.[28] Self-assessment of quality of life can change substantially from life periods of well-being to the dire period of NICU treatment. Unfortunately, this so-called "response shift" has hardly been investigated in neurocritical care. Fourth, the median time from admission to WOLST was quite short in almost the entire cohort, reflecting high disease severity and probably an institutional bias since many patients were referred from primary centers. This may have led to a delay in treatment initiation and is known to increase the odds of an unfavorable outcome and WOLST.[29] The high median NIHSS score of patients with stroke and the proportion of patients with mechanical ventilation also reflect a severely afflicted cohort with a poor prognosis for survival or a favorable outcome. Finally, our patient sample may have been too small to detect the impact of AD/HCP in a cohort with an overall high rate of early WOLST.

The finding that the presence of AD/HCPs was neither associated with the timing of WOLST nor associated with the treatment intensity may raise the question of whether the current concept of AD, in particular, can hold up to the expectations of patients and physicians in a setting of severe brain injury. The low frequency of AD/HCP in our patients (21.9%) may reflect a lack of acceptance of the AD concept in the aging population, despite the high mean age, distribution of relevant comorbidities, and reduced premorbid functional status (mRS score >2) in our cohort. Barriers to the expansion of ADs and the reluctance of patients to specify their EOL preferences in writing of ADs should be identified within the health-care system. Addressing this dilemma more thoroughly, however, is beyond the scope of our study. In summary, our results question the practical impact of AD/HCP in early NICU treatment. Scientific guidelines increasingly highlight the need to acknowledge time-limited ICU trials with a stepwise approach toward individualized prognosis, integrative palliative care, and early psychosocial support for surrogates and patients' families.[30,31] The emerging concept of "advance care planning" (ACP), which focuses on more comprehensive discussions of patient preferences with trained health-care professionals,[32] has been suggested to increase the AD/HCP prevalence and availability.[33] Further prospective NICU studies are urgently warranted on the applicability of ADs within the era of ACP.

Limitations

Our study has several limitations, mainly due to the shortcomings inherent to the analyses of routine clinical data. First and most relevant, our analysis is prone to information bias. Second, as a single-center study in the southwest region of Germany, where certain minorities are underrepresented and the average socioeconomic standards are higher than reported elsewhere, the rate of ADs and the findings on their impact may not be generalizable. Third, patients with noncerebrovascular diseases were underrepresented and the high treatment intensity of patients with vascular diseases may not be representative of other NICUs. Fourth, the small sample size may have masked differences between the groups, even though the clinical relevance of those smaller effects is debatable. Any differences in outcomes among patients with combined AD/HCP compared to those among patients with only AD or HCP could not be addressed due to the low numbers in the current study groups.

Finally, we only included patients who died after WOLST, which may present a selection bias. However, since the expected outcome of the WOLST decision is theoretically similar for each patient, we believe that the impact of this potential selection bias is limited.

Table 3. Cox Regression and Poisson Regression Analysis of Time Span.[a]

AD/HCP	N	IRR Model 1 (95% CI)	IRR Model 2 (95% CI)	HR Model 1 (95% CI)	HR Model 2 (95% CI)
Yes	68	1.15 (0.99-1.34), $P = .065$	1.10 (0.94-1.28), $P = .244$	1.03 (0.78-1.37), $P = .818$	1.03 (0.78-1.37), $P = .643$
No	242	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)

Abbreviations: AD, advance directive; CI, confidence interval; HCP, health-care proxy; HR, hazard ratio; IRR, incidence rate ratio; WOLST, withdrawal/withholding of life sustaining therapy.
[a]Neurointensive care unit admission to WOLST initiation, model 1: adjusted for age and sex; model 2: adjusted for age, sex, comorbidities (cancer, prior stroke, dementia, neurodegenerative disease), and prior setting of residence.

Conclusion

Our study neither revealed a significant association between AD/HCP and the timing of the decision to limit life-sustaining therapy nor with prior treatment intensity among neurocritical care patients with predominantly cerebrovascular disorders. The reasons for this lack of association, interpretation of its meaning, and further insights to the applicability and usefulness of AD/HCP in neurocritical care demand prospective research.

Authors' Note

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Conflicting Interests

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ORCID iD

Frank Stachulski https://orcid.org/0000-0002-5875-1005

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