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ORIGINAL ARTICLE

Early shunt surgery improves survival in idiopathic normal pressure hydrocephalus

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Abstract

Background and purpose: To examine the effect of delayed compared to early planning of shunt surgery on survival, in patients with idiopathic normal pressure hydrocephalus (iNPH), a long-term follow-up case–control study of patients exposed to a severe delay of treatment was performed.

Methods: In 2010–2011 our university hospital was affected by an administrative and economic failure that led to postponement of several elective neurosurgical procedures. This resulted in an unintentional delay of planning of treatment for a group of iNPH patients, referred to as $iNPH_{Delayed}$ (n = 33, waiting time for shunt surgery 6–24 months). These were compared to patients treated within 3 months, $iNPH_{Early}$ (n = 69). Primary outcome was mortality. Dates and underlying causes of death were provided by the Cause of Death Registry. Survival was analysed by Kaplan–Meier plots and a Cox proportional hazard model adjusted for potential confounders.

Results: Median follow-up time was 6.0 years. Crude 4-year mortality was 39.4% in $iNPH_{Delayed}$ compared to 10.1% in $iNPH_{Early}$ (p = 0.001). The adjusted hazard ratio in $iNPH_{Delayed}$ was 2.57; 95% confidence interval 1.13–5.83, p = 0.024. Causes of death were equally distributed between the groups except for death due to malignancy which was not seen in $iNPH_{Delayed}$ but in 4/16 cases in $iNPH_{Early}$ (p = 0.044).

Conclusions: The present data indicate that shunt surgery is effective in iNPH and that early treatment increases survival.

KEYWORDS
ataxia and gait disorders, case–control study, cognitive disorders and dementia, normal pressure hydrocephalus

INTRODUCTION

Idiopathic normal pressure hydrocephalus (iNPH) is a treatable yet underdiagnosed disorder. The prevalence has been estimated at 2% of persons aged 70 years or older [1]. Despite a continuous rise in the incidence of shunt surgery for iNPH in Sweden [2] the majority of persons suffering from iNPH do not receive treatment.

Based on uncontrolled observational studies, shunt surgery improves symptoms in around 80% of patients [3]. Two randomized controlled trials have shown that shunt surgery is effective [4,5] but data from controlled studies are considered scarce [6].

Furthermore, the effect of treatment on survival has not been reported previously.

This observational study is based on circumstances in which a random group of iNPH patients were unintentionally exposed to a severe treatment delay. The Sahlgrenska University Hospital, Gothenburg, Sweden, was affected by administrative and economic failure in 2010–2011, leading to postponement of elective neurosurgical procedures, and several iNPH patients were left on the waiting list for up to 2 years. In 2011 additional financial support enabled elimination of the queues, and all patients who had been waiting for more than 6 months (n = 33; $iNPH_{Delayed}$) were included in a study published in 2013 [7]. They were followed up and compared to all patients in the local hydrocephalus registry who had been operated within 3 months in 2004–2012 (n = 69; $iNPH_{Early}$). The present study is a long-term follow-up of these patients, with the specific aim of studying the effect of delayed compared to early planning of shunt surgery on survival.

METHODS

The study sample of in total 102 iNPH patients scheduled for shunt surgery in 2004–2012 and their 3-month postoperative outcome has been described in detail previously [7]. An overview is presented in Figure 1.

Diagnosis of iNPH

All patients were evaluated at the same clinic by the same routine clinical work-up including brain imaging with magnetic resonance imaging and/or computed tomography and examination by a physician, a neuropsychologist and a physiotherapist. Severity of symptoms was assessed using a validated iNPH scale where tests for gait, balance, cognitive abilities and urinary symptoms yield a composite score of 0–100 [8]. Additionally, the modified Rankin Scale (mRS) and the Mini-Mental State Examination (MMSE) were recorded. Ancillary tests, such as the cerebrospinal fluid (CSF) tap test or infusion tests, were performed when considered clinically indicated. The diagnosis of iNPH was made in accordance with the international guidelines [9]. The decision to refer for shunt surgery was made in routine multidisciplinary conferences; the date of this decision is the baseline date in this study.

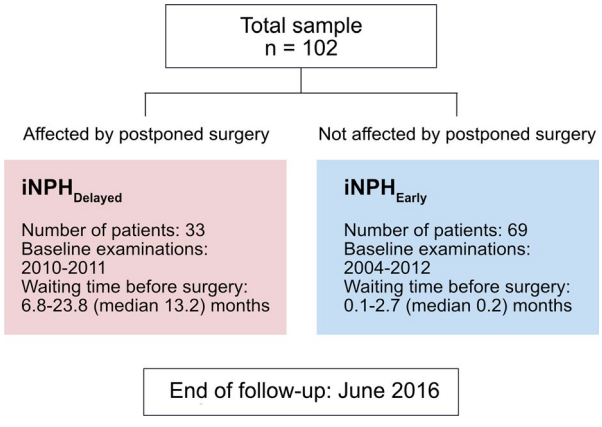

FIGURE 1 Overview of the study sample and treatment groups

Baseline characteristics for both groups, and data from the second preoperative investigations performed only in the $iNPH_{Delayed}$ group, are shown in Table 1. Patients in $iNPH_{Delayed}$ were older, and hypertension was more common in this group. There were no significant differences between the groups regarding any other baseline characteristics.

Clinical course

All but one patient underwent shunt surgery; one patient in $iNPH_{Delayed}$ died before surgery was performed, after 14 months' wait. The number and types of postoperative complications were recorded. Complications were classified as minor or major. Minor complications were defined as complications that did not cause significant disability and did not require additional surgeries: postural headaches, smaller subdural effusions or hygromas which resolved after adjustment of the shunt valve. Major complications were defined as complications that required additional surgery or caused significant disability: larger subdural haematomas, obstruction or infection of the shunt catheter, stroke, intracerebral haemorrhage or postoperative epilepsy.

Assessment of outcome

The primary outcome was mortality. Dates and causes of death until 17 June 2016 were commissioned from the Swedish Cause of Death Registry (CDR). The CDR is governed by the National Board of Health and Welfare, who apply an internationally used algorithm [10] to define which is the underlying cause of death—that cause is reported in this study.

The underlying causes of death, classified as ICD-10 diagnostic codes, that were represented in the study were grouped as pneumonia J18.9; malignant disease C259, C494, C679, C80; dementia F019, F03, F039; neurological disease B91, G20, G239; hydrocephalus G919; cardiovascular disease I10, I110, I219, I251, I259, I509, I713; cerebrovascular disease I619, I64; and fall accident W18.

Statistical analysis

Proportions were compared by Fisher's exact test and the Mann–Whitney U test was used for comparison of categorical or continuous variables.

Survival analyses were performed with Kaplan–Meier plots, the log-rank test and Cox regression analysis. The proportional hazards assumption was assessed by goodness-of-fit tests and visual analysis of plots of scaled Schoenfeld residuals against time.

TABLE 1 Baseline data, median follow-up times and complication rates

	$iNPH_{Delayed}$ (n = 33)		$iNPH_{Early}$ (n = 69)	
	Baseline preoperative investigation (Preop 1)	**Second preoperative investigation (Preop 2)**	**Baseline preoperative investigation (Preop 1)**	p[a]
Age, years, median (min–max)	76 (55–89)	78 (56–90)	70 (48–84)	0.006
Women, *n* (%)	16 (48)		32 (46)	1.0
MMSE, median (min–max)	25 (14–30)	22 (9–30)	25 (9–30)	0.42
Modified Rankin Scale, median (min–max)	2 (1–4)	3 (1–5)	2 (1–4)	0.50
Total iNPH scale score, median (min–max)	45 (7–94)	37 (5–95)	49 (2–95)	0.16
Duration of symptoms, months, median (min–max)	24 (8–132)		24 (6–360)	0.70
Hypertension, *n* (%)	20 (61)		24 (35)	0.019
Diabetes, *n* (%)	4 (12)		10 (14)	1.0
Cardiovascular disease, *n* (%)	10 (30)		12 (17)	0.20
Waiting time before surgery, months, median (min–max)	13.2 (6.8–23.8)		0.2 (0.1–2.7)	<0.001
Follow-up time, years, median (IQR)	5.4 (2.7–5.7)		7.4 (4.7–8.6)	<0.001
Patients with major complications, *n* (%)	7 (20.6)		20 (29.0)	0.48
Patients with minor complications, *n* (%)	3 (8.8)		10 (14.5)	0.54

Abbreviations: iNPH, idiopathic normal pressure hydrocephalus; IQR, interquartile range; MMSE, Mini-Mental State Examination.

[a] For baseline data, p values represent comparisons between Preop 1 in both groups.

Before entry into Cox regression analysis the mRS was dichotomized at the median whilst MMSE and the iNPH scale score were used as continuous variables.

All variables with a significance level $p < 0.05$ in univariable analyses were included in a multivariable analysis with a forward stepwise approach. In this analysis, age, group (early or delayed surgery), iNPH scale score and MMSE were included, but the latter two were rejected as they did not reach significance in the stepwise forward model.

Age-stratified Cox regression analyses were also performed. Additionally, after stratification of patients into age up to or above 75 years and into baseline mRS 1–2 or mRS 3–4, univariate Cox regression analyses were performed, and Kaplan–Meier curves were plotted, to analyse the effect of delayed surgery in these subgroups.

Patients in $iNPH_{Delayed}$ were older than those in $iNPH_{Early}$. Therefore, the Kaplan–Meier curves were replotted after controlling for the possible effect of age differences in the following way: in $iNPH_{Early}$ the six patients younger than 55 years were excluded, and in $iNPH_{Delayed}$ the four patients aged above 84 years were excluded. This resulted in age ranging from 55–84 years in both groups and a median age of 71 years in $iNPH_{Early}$ and of 72 in $iNPH_{Delayed}$, $p = 0.18$.

Statistical analyses were performed using SPSS version 24 for Windows and Stata version 14.0 IC.

RESULTS

Median follow-up time for the total sample was 6.0 years, interquartile range 4.3–7.8, shorter for $iNPH_{Delayed}$ and longer for $iNPH_{Early}$ (Table 1).

At the end of follow-up, 23% (n = 16) of the patients in $iNPH_{Early}$ had died, compared to 52% (n = 17) of those in $iNPH_{Delayed}$ (p = 0.006). The crude 4-year mortality was 39.4% in $iNPH_{Delayed}$, compared to 10.1% in $iNPH_{Early}$ (p = 0.001). Additionally, the crude and age-adjusted Kaplan–Meier survival curves both showed significantly higher mortality in $iNPH_{Delayed}$ (Figure 2).

Specifically, the higher risk of dying when exposed to delayed planning of surgery was seen for older patients, aged above 75 years, but could not be seen for patients aged up to 75 years (Table 2). Patients were also subgrouped based on their degree of disability, and patients with mRS 1–2 and with mRS 3–4 both had a higher risk of dying if exposed to delayed planning of surgery (Table 2). The corresponding Kaplan–Meier curves and log-rank tests for these subgroup analyses are shown in Figure S1.

The iNPH scale score and the MMSE score were independent significant predictors for mortality, with a 15% lower mortality per 5 points higher score on the iNPH scale and a 46% lower mortality per 5 points better MMSE in univariate Cox regression analysis. However, no other factors than age and whether patients belonged

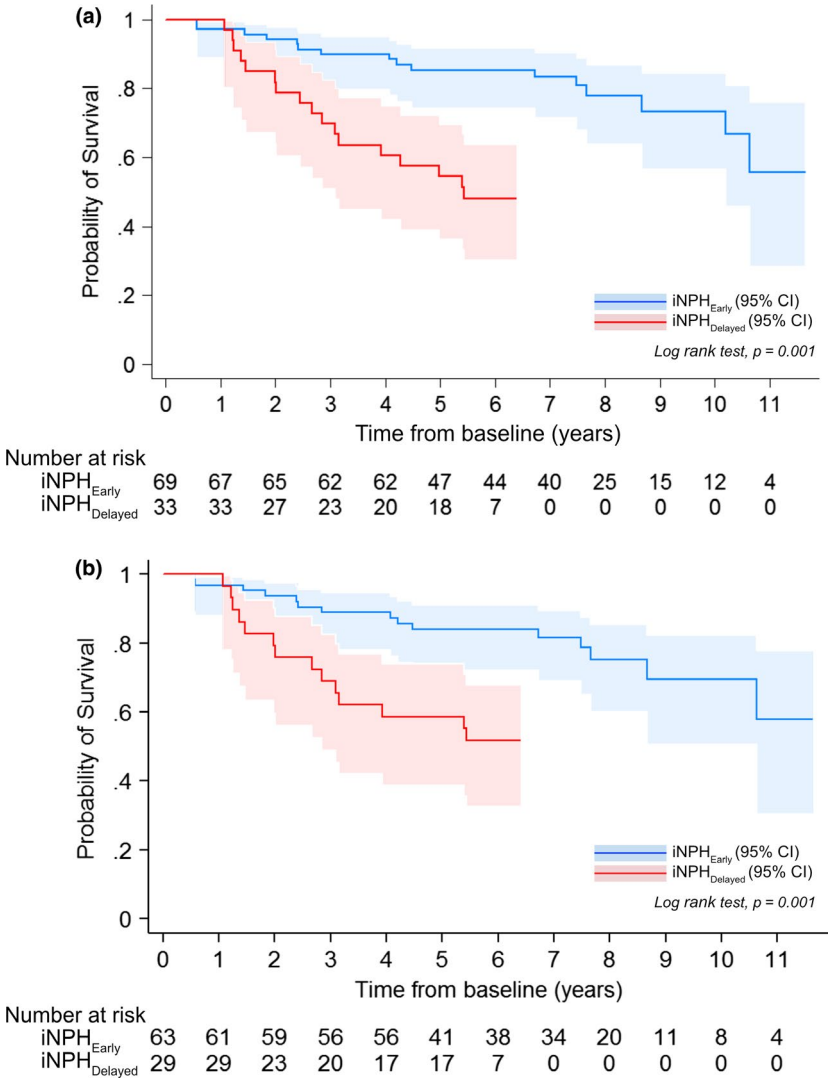

FIGURE 2 Survival in iNPH patients with delayed or early treatment. In (a) all patients are included. In (b) the groups have been adjusted for age by exclusion of the youngest patients in $iNPH_{Early}$ and the oldest patients in $iNPH_{Delayed}$. After this adjustment, the age range in both groups was 55–84, median age 71 in $iNPH_{Early}$ and 72 in $iNPH_{Delayed}$, $p = 0.18$

to $iNPH_{Delayed}$ or $iNPH_{Early}$ were significant predictors of mortality in the multivariable model (Table 3). The hazard ratio (HR) for death in $iNPH_{Delayed}$ was 2.57 (95% confidence interval 1.13–5.83, $p = 0.024$). On performing age-stratified Cox regression analysis, a similar result was seen: only delayed vs. early surgery was of significance for survival, with HR 2.85 (95% confidence interval 1.04–7.84, $p = 0.042$) (Table 3).

If the multivariable model was widened to include all variables reaching significance level $p < 0.1$ in univariable analyses, also mRS and cardiovascular disease were included, but none of these reached significance in the multivariable model and the final result was not changed.

The complication rates did not differ significantly between the two groups (Table 1).

Death caused by malignant disease was seen in four of the 16 deceased patients in $iNPH_{Early}$ but in no case in $iNPH_{Delayed}$, $p = 0.044$. For other causes there were no significant differences (Table 4). The underlying cause of death in the CDR for the patient who died before shunt surgery was performed was hydrocephalus.

DISCUSSION

The effect of delayed planning of shunt surgery on survival has not been reported previously. Mortality in iNPH patients unintentionally exposed to delayed planning of treatment was examined compared to those treated within a normal time frame. It was found that patients with delayed treatment had a more than twofold increased risk of death, despite having eventually undergone shunt surgery (all but one) and despite benefitting equally from surgery 3 months postoperatively to the group treated without delay [7]. The present data suggest that shunt surgery is effective; specifically, that early treatment increases survival compared to delayed treatment. These findings are important for the clinical management of iNPH patients.

The finding that patients who were exposed to delayed treatment had an excess mortality remained after controlling for the independently significant factors, including age and severity of symptoms. There was a slightly higher frequency of complications in $iNPH_{Early}$, probably explained by their longer follow-up time, but the

TABLE 2 Cox regression analysis of the time to death for patients with delayed compared to early surgery, stratified by level of disability (mRS 1–2 vs. 3–4) and by age at time of diagnosis (48–75 vs. 76–89 years)

		Death	Non-death	Total	HR	95% CI	*p*
mRS[a] 1–2, *n* = 59	$iNPH_{Delayed}$	7	11	18	3.01	1.14–7.94	0.026
	$iNPH_{Early}$	9	32	41			
	Total for mRS 1–2	16	43	59			
mRS[a] 3–4, *n* = 43	$iNPH_{Delayed}$	10	5	15	6.56	1.69–25.41	0.007
	$iNPH_{Early}$	7	21	28			
	Total for mRS 3–4	17	26	43			
Age 48–75, *n* = 65	$iNPH_{Delayed}$	3	13	16	1.84	0.44–7.69	0.41
	$iNPH_{Early}$	7	42	49			
	Total for age 48–75	10	55	65			
Age 76–89, *n* = 37	$iNPH_{Delayed}$	14	3	17	4.66	1.66–13.03	0.003
	$iNPH_{Early}$	9	11	20			
	Total for age 76–89	23	14	37			

Note: The scores 0 or 5 were not represented in the patients at Preop 1.

Abbreviations: CI, confidence interval; HR, hazard ratio; iNPH, idiopathic normal pressure hydrocephalus; mRS, modified Rankin Scale.

[a] mRS, modified Rankin Scale at the first preoperative investigation, Preop 1.

TABLE 3 Cox regression analyses of baseline variables' influence on survival

	Univariable analysis			Multivariable analysis (stepwise forward)			Age-stratified analysis		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Group, delayed vs. early	4.24	1.94–9.27	<0.001	2.57	1.13–5.83	0.024	2.85	1.04–7.84	0.042
Age	1.15	1.09–1.21	<0.001	1.13	1.07–1.18	<0.001	–	–	–
Sex, male	1.50	0.74–3.00	0.26				1.50	0.55–4–09	0.43
Symptom grading									
MMSE score/5	0.54	0.39–0.76	<0.001		ns		0.67	0.41–1.09	0.11
mRS (3–4 vs. 1–2)	2.02	0.99–4.12	0.055				1.31	0.50–3.48	0.59
iNPH scale score/5	0.85	0.78–0.93	<0.001		ns		0.89	0.76–1.03	0.12
Duration of symptoms, months	1.00	1.00–1.01	0.63				0.99	0.98–1.01	0.48
Comorbidities									
Hypertension	1.24	0.62–2.46	0.55				1.06	0.39–2.92	0.91
Cardiovascular disease	1.91	0.90–4.08	0.092				1.79	0.53–5.97	0.35
Diabetes	0.63	0.19–2.07	0.50				1.21	0.25–5.86	0.82

Abbreviations: CI, confidence interval; HR, hazard ratio; iNPH, idiopathic normal pressure hydrocephalus; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale.

frequency did not differ significantly between the groups, hence not explaining the difference in mortality.

Subgrouping the 102 patients, a difference in survival was seen for patients with early or delayed surgery regardless of functional disability as measured by mRS. Further, this difference could be seen in older patients above 75 years of age. Any difference in survival related to delayed surgery for patients with a longer life expectancy, aged up to 75 years, could not be detected in this sample. Based on these results, it is of extra importance to avoid unnecessary waiting for older iNPH patients.

According to several uncontrolled observational studies, shunt surgery may improve symptoms and decrease disability in most patients [3]. Randomized controlled trials by Kazui et al. [5] and Tisell et al. [4] have also shown clinical effects. However, practice guidelines issued by the American Academy of Neurology in 2015 [6] concluded that shunt surgery might be beneficial for patients with iNPH but that high-level evidence is lacking. It would be difficult to examine the effect of shunting on survival using a randomized controlled trial considering the ethical implications and need

TABLE 4 Causes of death

Cause of death	$iNPH_{Delayed}$, *n* (%)	$iNPH_{Early}$, *n* (%)	*p*
Pneumonia	1 (5.9)	1 (6.3)	1
Malignant disease	0	4 (25)	0.044
Dementia	4 (24)	4 (25)	1
Neurological disease	3 (18)	0	0.23
Hydrocephalus	1 (5.9)	0	1
Cardiovascular disease	4 (24)	6 (38)	0.47
Cerebrovascular disease	3 (18)	1 (6.3)	0.60
Fall accident	1 (5.9)	0	1
Total	17	16	

Abbreviation: iNPH, idiopathic normal pressure hydrocephalus.

for extended follow-up. In contrast, whilst our results are based on unwanted events, the observational nature of this study allowed us to examine outcomes after more than half a decade. Therefore, these results might add important data to existing evidence, supporting the notion that shunting has substantial effects in iNPH.

There are several possible explanations of why patients with early shunt surgery have lower mortality. First, during delay, iNPH patients will suffer from a continuous overall deterioration with increased disability, leading to, for example, a risk of falls, loss of self-mobilizing capacity, infections and malnutrition. Secondly, iNPH is related to vascular risk factors and cerebral white matter lesions [11] which have been found to decrease after CSF diversion, with reductions correlating with clinical improvement [12]. Furthermore, and congruently, CSF diversion seems to be related to increased cerebral perfusion [13,14]. Thus, it is plausible that early treatment with shunt surgery leads to an improved cerebral microcirculation, especially in the periventricular area, which is probably of importance for the function of the brain and could lead to a lower risk of death [15]

Data concerning causes of death are far from exact, since such causes are established by physicians in different situations. The only difference that could be found between the two groups was that there were more deaths due to malignancies in $iNPH_{Early}$, four out of 16 deaths, whereas there were none in $iNPH_{Delayed}$. A possible explanation for this finding is that patients who had shunt surgery in a timely fashion lived longer and therefore had the time to develop and be diagnosed with malignancies.

There are important limitations to this study that should be discussed. The main limitation is the observational design. Although it may be supposed that patients were affected by the treatment delay at random, the possibility that patients in the delayed treatment group had some underlying propensity that ultimately affected outcome cannot be fully ruled out. Despite having adjusted for several potential confounders there is still a risk of residual confounding or unknown sources of bias affecting the results.

Another major limitation is the difference in age between the two groups (median 70 vs. 76 years). Compiling data for $iNPH_{Delayed}$, and retrospectively selecting other patients with early performed surgery within 3 months from the local database, for the case–control design of the original study, it was surprising to find that head-to-head matching was not possible due to overweight of more elderly patients in $iNPH_{Delayed}$. To deal with this as correctly as possible, all patients operated between 2004 and 2012 without delay, that is, within 3 months, were included rendering patient groups similar with regard to other important aspects such as baseline symptom severity and duration of symptoms.

In the present study, the effect of $iNPH_{Delayed}$ patients being older was adjusted for by adding age into the multivariable Cox regression analysis and this was complemented by age-stratified Cox regression analyses. Additionally, the Kaplan–Meier plot was adjusted for age by excluding the oldest patients from $iNPH_{Delayed}$ and the youngest from $iNPH_{Early}$.

During the years, patients' degree of priority in the queue could be adjusted according to decisions of individual surgeons, based on information from patients or their relatives. Mainly such information would indicate deterioration leading to frequent falls. However, it is important to emphasize that patients in $iNPH_{Delayed}$ were never intentionally deprioritized, nor did they themselves choose to postpone treatment. The intention of all involved personnel was to provide the best possible care during these highly unfortunate circumstances.

The relatively small sample size is also a limitation. $iNPH_{Delayed}$ included only 33 patients, and a larger sample could probably have provided more precise outcome estimates. However, the total sample size of this study was 102, making it larger than many studies in iNPH.

A Swedish registry study showed that the HR for iNPH patients compared to the general population was 1.8 [16]. Patients in $iNPH_{Early}$ had surgery within an exceptionally short time frame (median 6 days from decision). Therefore, these patients probably had better survival than iNPH patients in general, closer to the survival of the general population, whilst $iNPH_{Delayed}$ probably had poorer survival than iNPH patients in general, due to the waiting time. However, as a significant treatment effect was seen on a group level also in $iNPH_{Delayed}$ [7] presumably the mortality of that group is lower than in untreated persons with iNPH [17].

Our study implies that at the point where symptoms are serious enough to justify an investigation for iNPH and, subsequently, a decision of shunt surgery, the patients are at large risk of earlier death if that surgery is postponed. This difference was specifically seen in older patients above 75 years of age, implying that especially for these patients unnecessary wait should be avoided. In the assessment of iNPH patients, the risks of shunt surgery must be taken into consideration—but this study adds evidence that so should the risks of postponing surgery.

CONCLUSION

During a follow-up of more than 5 years, it was found that patients exposed to delayed planning of shunt surgery had an increased risk

of death, by an HR of 2.57. These results support that shunt surgery is effective and that early treatment increases survival.

CONFLICT OF INTEREST

Dr Wikkelsø has received an honorarium for lecturing by Codman, Integra. Drs Andrén, Hellström, Tullberg and Jaraj report no disclosures.

AUTHOR CONTRIBUTIONS

Kerstin Andrén participated in the design and conceptualization of the study, collected the data, performed the statistical analyses, interpreted the results and drafted the manuscript. Carsten Wikkelsø, Per Hellström and Mats Tullberg participated in the design of the study, interpretation of data, and revision of the manuscript. Daniel Jaraj conceived the study, participated in the design, collected the data, performed the statistical analyses, interpreted the results and drafted the manuscript.

ETHICAL STATEMENT

The study was approved by the Regional Ethical Review Board in Gothenburg (Dnr 009–13).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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