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The Luigi Sacco Hospital VAS-COG stroke care pathway: A five-year experience

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ABSTRACT

Background: Psycho-cognitive consequences are a frequent cause of disability in stroke survivors but are often underdiagnosed also because of lack of services dedicated to these aspects. We started assessing systematically cognitive and behavioral functions in acute stroke patients and to follow them up. Here, we report a retrospective analysis of the organization of the Sacco VAS-COG stroke care pathway and the refinements implemented during 5 years of activity.

Methods: The protocol includes baseline collection of clinical history, general and neurologic examinations, functional, neuropsychological, and neuroimaging assessment. At follow-up, a diagnosis of cognitive decline was made based on best clinical judgment in the first period (January 2018 to May 2019, namely VAS-COG protocol 1.0) and then based on an extensive neuropsychological battery (May 2019 to January 2023, namely VASCOG protocol 2.0); psychiatric and behavioral disturbances are investigated through suitable scales.

Results: From January 2018 to December 2022, 834 patients (mean age 76±13.6 years; 46.6 % females) with acute cerebrovascular events were admitted to the stroke unit, mostly (80 %) for ischemic strokes. Pre-event cognitive impairment was not assessable in 78 patients (9.3 %) because no reliable informant was present and was reported in 327/756 (43 %) patients. During follow-up, post-stroke cognitive impairment was detected in 124/217 (57.1 %) patients in VAS-COG protocol 1.0 and in 137/201(68.2 %) patients in VAS-COG protocol 2.0, while 95/218 (43.2 %) patients were found to be depressed and patients presented on average 2.5 neuropsychiatric symptoms on Neuropsychiatric Inventory-questionnaire.

Conclusions: The VAS-COG stroke care pathway represents a model for patients and for their families.

Introduction

Post-stroke cognitive impairment (PSCI) represents a subtype of the larger chapter of vascular cognitive impairment and refers to the cognitive decline that occurs following an ischemic or a hemorrhagic stroke [1]. Epidemiological studies report that a history of stroke doubles the risk of dementia incidence in individuals over 65 years of age and that PSCI frequency increases after recurrent strokes and as patients move temporally away from the stroke [2]. The association between stroke and cognitive impairment cannot be explained solely by the presence of cardiovascular risk factors or demographic variables or by the presence of cognitive impairment pre-existing the cerebrovascular event. In the end, most stroke survivors will experience some degree of cognitive impairment. Despite these impressive figures, almost all current efforts of stroke neurologists are dedicated to acute treatments of patients, even if only a minority of patients are nowadays able to benefit from these treatments [3] (Fig. 1).

More recently, the attention to PSCI has increased and international guidelines recommend a neuropsychological assessment for all stroke survivors [4,5]. Neuropsychiatric symptoms such as depression and anxiety are also very frequent and neglected chronic disturbances following a stroke [6]. Clinics dedicated to patients at risk for neuropsychiatric consequences of stroke, therefore, would represent an important service to implement screening, diagnostic, and global treatment of cerebrovascular diseases.

Under this light, we started a program dedicated to the psycho-cognitive evaluation of all patients admitted to our stroke unit. This program includes a bedside assessment during the acute phase and a

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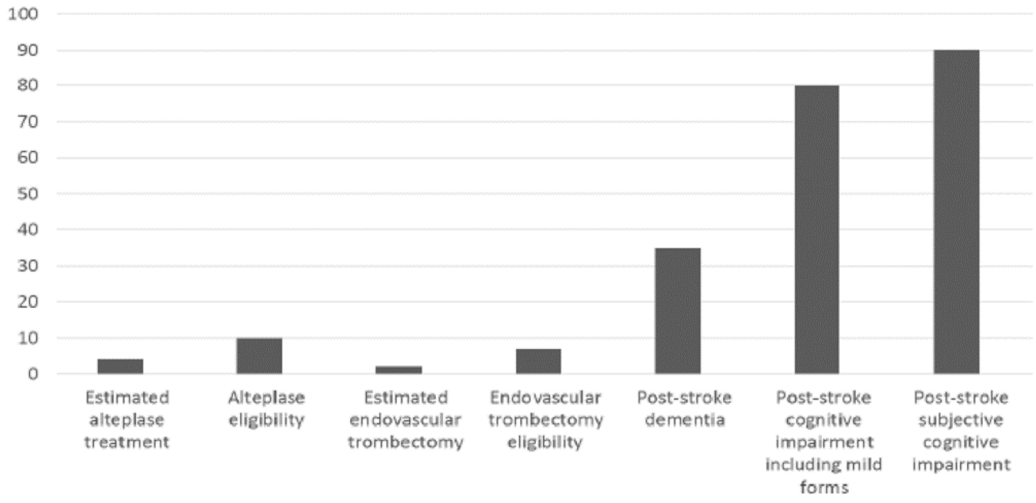

Fig. 1. Comparison of frequency of use of acute stroke treatments and of cognitive sequelas of stroke.

follow-up consisting of scheduled visits aimed at identifying cognitive, psychiatric, and behavioral disturbances caused or associated with stroke. We called the out-patient service "VAS-COG clinic" inspired by a previous Italian experience of the Florence VAS-COG clinic [7], whose name derives from that of the International Society for Vascular Behavioural and Cognitive Disorders.

In this paper, we have focused on:

1) describing the general organization of the service over 5 years of activity
2) reporting all the refinements of our protocol over time
3) describing our casuistry with the intention of illustrating its representativeness

Methods

Participants were consecutive inpatients admitted to Luigi Sacco hospital stroke unit with an acute cerebrovascular disease event since January 2018 (ischemic strokes, hemorrhagic strokes, transient ischemic attacks, subarachnoid hemorrhages, cerebral venous thrombosis, and other rarer cerebrovascular disorders).

This unit is the only one in the referral area (north-west area of Milan) admitting patients with acute stroke unless they need orotracheal intubation. At baseline, in the stroke unit (on average, within 7 days of stroke), all patients underwent an extensive evaluation following a standardized diagnostic protocol (VAS-COG protocol 1.0).

This included collection of clinical history, medical and neurological examinations, accompanied by laboratory testing, neuroimaging, and a brief neuropsychological assessment. During the neuropsychological briefing with the caregiver, information about pre-stroke cognitive status is collected and it is explained that patients will be followed up in the outpatient clinic and care will not be limited to the days of hospitalization. The date of the follow visit is provided at discharge. When possible, we call patients before follow-up visits to remind them of the appointment for the visit.

The staff involved in the service was initially composed of a certified neurologist and residents in neurology with a specific interest and training in cerebrovascular diseases and dementia; beginning with May 2019, a second certified neurologist and two neuropsychologists were also involved. Contemporaneously, the VAS-COG protocol was revised (VAS-COG protocol 2.0). The following amendments were made to the original protocol: 1) cognitive status prior to the cerebrovascular event and the definition of pre-stroke cognitive impairment was based on Frontotemporal Lobar Degeneration-Modified Clinical Dementia Rating (FTLD-CDR) Scale global score in VAS-COG protocol 1.0 (cut-off for cognitive impairment ≥ 0.5) [8], and on the Informant questionnaire on cognitive decline in the elderly (IQCODE) in VAS-COG protocol 2.0 (cut-off for dementia >3.3) [9]; both scales were administered by the neurologists and/or by the neuropsychologists; 2) neuropsychological evaluation at bedside consisted of Montreal Cognitive Assessment (MoCA) Basic and Clock Drawing Test (CDT) in VAS-COG protocol 1.0 [10,11] and of MoCA in VAS-COG protocol 2.0 (which included CDT as a subtest); 3) the diagnosis of PSCI based on the evaluating neurologist's best clinical judgment in VAS-COG protocol 1.0 was supplemented by an extensive neuropsychological examination in VAS-COG protocol 2.0. Performances at second level cognitive tests were evaluated according to national normative studies that applied an equivalent score (ES) methodology. ES is a non-parametric (percentiles based) norming method that allows to convert age and education adjusted scores into an ordinal 5-point scale: ES=0, impaired performance (a demographically adjusted score below the outer confidence limit for the 5th centile of the normal population); ES=1, borderline performance (a demographically adjusted score within the inner and outer confidence limits for the 5th centile of the normal population); ES=2, 3 and 4, normal performance [12]. The diagnosis of PSCI was achieved when at least 2 neuropsychological tests resulted impaired (PE=0) or borderline (PE=1).

The application of two protocols overlapped for a short period (the month of May 2019) in that patients were evaluated at baseline (stroke unit stay) with the old protocol and at follow-up with the new one [13]. The entry of neuropsychologists into the team made it possible to extend and postpone to 6 months the neuropsychological investigation that in the first protocol was carried out exclusively by the neurologist during the usual neurological clinical follow-up visit scheduled at 3 months from the acute event. Moreover, an assessment of neuropsychiatric symptoms with Neuropsychiatric Inventory-questionnaire (NPI-q) [14] was repeated at 6 months and the presence of depressive and anxiety symptoms were investigated through the use of Center for Epidemiological Studies Depression scale (CES-D) [15] and Self-rating Anxiety Scale (SAS) [16] respectively.

Neurologists provide contacts (telephone and/or email) for all patients enrolled and during outpatients clinics provide information on psycho-cognitive consequences of stroke, organize neuropsychological evaluations at 6 months from the stroke (in the VAS-COG 2.0 protocol) and follow-up neurological visits few weeks later to discuss results of the neuropsychological battery and to propose, if necessary, treatment for depressive, anxiety, or behavioral disorders.

In VAS-COG protocol 1.0, at follow up the neurologist collected the following data: NIHSS, mRS, evaluation of vascular risk factor control (weight, alcohol consumption, smoking habit), cognitive and functional measures (MoCA Basic [17], CDT [18], FTLD-modified CDR [8], ADL

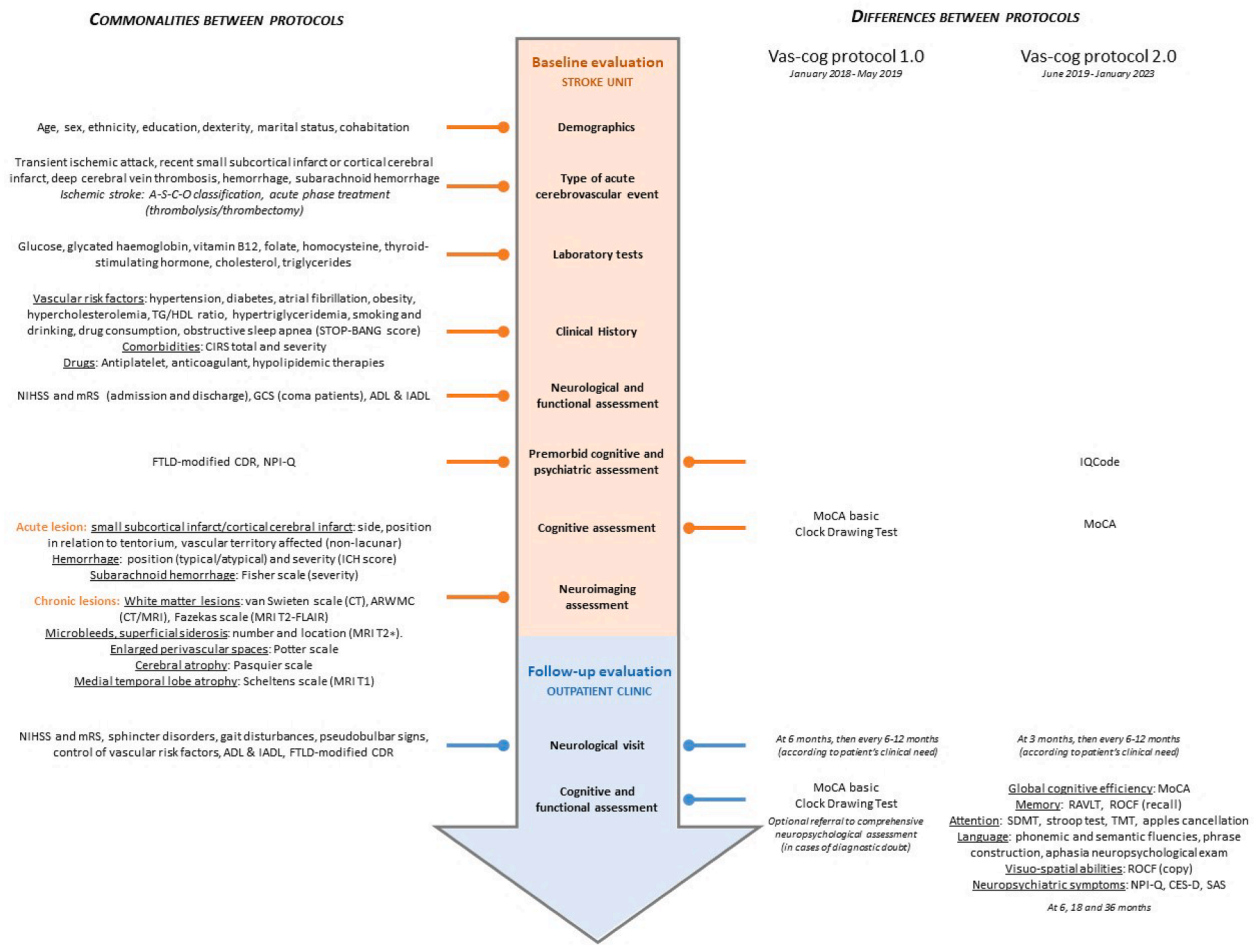

Fig. 2. Stroke care pathway (VAS-COG protocol 1.0 and 2.0).
List of abbreviations ADL=activity of daily living scale; ARWMC=age-related white matter changes; A-S-C-O=Atherosclerosis, Small-vessel disease, Cardiac pathology; Other causes [37]; CES-D=center for epidemiological studies depression scale; CIRS=Cumulative illness rating scale; FLTD-CDR=frontotemporal lobar degeneration modified clinical dementia rating scale; GCS=Glasgow coma scale [38]; IADL=instrumental activity of daily living scale; ICH=intracerebral hemorrhage; IQCODE=informant questionnaire on cognitive decline in the elderly; MOCA=montreal cognitive assessment; MRS=modified rankin scale [39]; NIHSS=national institutes of health stroke scale [40]; NPI-Q=neuropsychiatric inventory questionnaire; RAVLT=rey auditory verbal learning test; ROCF=rey–osterrieth complex figure; SAS=self-rating anxiety scale; SDMT=symbol digit modalities test; STOP-BANG=Snore, Tired, Observed Apneas, Pressure, BMI,Age, Neck Circumference, Gender [41] TG/HDL Ratio=triglycerides/high density cholesterol ratio [42]; TMT=trail making test.

[19], IADL [20]); presence of sphincter disorders, gait disturbances, and pseudobulbar signs was recorded as 'present' on chart only when documented in clinical notes; cognitive and functional measures were subsequently extracted from the neurological examination and evaluated during the neuropsychological assessment at 6 months in VAS-COG protocol 2.0.

Fig. 2 shows the stroke care pathway including commonalities and differences between two different phases of our protocol (VAS-COG protocol 1.0 and 2.0), including neuroimaging assessment [21–27] and the cognitive tests of the neuropsychological battery used at follow up in VAS-COG protocol 2.0 [28–36].

Admission of patients to the stroke unit was temporarily stopped between March and August 2020 and between November 2020 and October 2021 because of the COVID-19 pandemic reorganization of the service. Here we report a retrospective analysis of clinical data.

Results

From January 2018 to December 2022, 834 patients were admitted to the stroke unit for an acute cerebrovascular event. Table 1 shows their sociodemographic characteristics.

Seventy-eight patients (9.3 %) were not assessed for pre-morbid cognitive impairment because no caregiver or reliable informant was present during the stroke unit stay. A pre-event cognitive impairment (mild or major) based on FLTD-CDR was recognised in 327/756 (43 %) of patients admitted to the stroke unit. In VAS-COG protocol 2.0, a pre-stroke dementia, based on the IQ-code, was found in 153/432 (35.4 %) patients; using FLTD-CDR 187/432 (43.3 %) patients had a score $\geq$0.5 and 84/432 (19.4 %) patients had a score $\geq$1.

The most frequent cause of admission to the stroke unit was an ischemic stroke (667/834, 80 % of patients). Three-hundred-forty-two patients underwent only a CT scan (41 %), 492 underwent both CT and MRI scans (59 %) within a few days of the index event (maximum 7 days).

Fifty-three patients (6.4 %) died during hospitalization.

Cognitive evaluation at bedside of stroke was performed after 4.64 $\pm$ 3.36 days from the acute event.

Four-hundred eighty-seven (58.4 %) patients were adherent to clinical follow-up (attending at least one visit at the outpatient clinic) with a mean follow-up time of 13.9 months. We were notified of the deaths of 74 patients among those who did not return to follow-up.

Patients who did not return to the follow up were less educated (9.2 $\pm$ 5.1 vs. 9.4 $\pm$ 4.3 years of education, $p < 0.001$) and had the following worst scores: premorbid mRS (1.49 $\pm$ 1.61 vs. 0.48 $\pm$ 1.01, $p < 0.001$),

Table 1
Sociodemographic and clinic characteristics of patients evaluated in VAS-COG activity.

	VAS-COG (all protocols) $N = 834$	VAS-COG protocol 1.0 $N = 360$	VAS.COG protocol 2.0 $N = 474$
Sex (female %)	389 (46.6)	206 (57.2)	183 (38.6)
Age, yrs	76 ± 13.6	76 ± 12.0	75 ± 14.0
Education, yrs	9.2 ± 4.6	8.7 ± 4.2	9.7 ± 4.8
Premorbid mRS			
mRS 0	541 (64.9)	234 (65.0)	307 (64.8)
%mRS 1	62 (7.4)	34 (9.4)	28 (5.9)
mRS ≥ 2	231 (26.7)	92 (25.5)	139 (29.3)
Pre-event cognitive impairment*	327 (43.2)	140 (43.2)	187 (43.3)
FLTD-CDR ≥ 0.5	191 (25.2)	88 (27.1)	103 (23.8)
Mild cognitive impairment	136 (17.9)	52 (16.0)	84 (19.4)
FLTD-CDR = 0.5	N/A	N/A	153 (35.4)
Dementia			
FLTD-CDR ≥ 1			
IQCODE > 3.3			
Type of CVD			
TIA	70 (8.4)	37 (9.7)	33 (7.0)
Ischemic stroke	667 (80.0)	288 (80.0)	379 (79.9)
Hemorrhagic stroke	78 (9.3)	25 (6.9)	53 (11.2)
Subarachnoid hemorrhage	10 (1.2)	6 (1.7)	4 (0.8)
Cerebral venous thrombosis	4 (0.5)	2 (0.5)	2 (0.4)
Other	2 (0.2)	1 (0.3)	1 (0.2)
	3 (0.3)	1 (0.3)	2 (0.4)
NIHSS at presentation (only for ischemic stroke)	6.3 ± 6.5	7.0 ± 7.0	5.9 ± 6.1
mRS at discharge			
- mRS 0	220 (26.4)	92 (25.6)	128 (27.0)
- mRS 1	170 (20.4)	91 (25.3)	79 (16.7)
- mRS 2	109 (13.1)	31 (8.6)	78 (16.5)
- mRS 3	92 (11.0)	31 (8.6)	61 (12.9)
- mRS 4	107 (12.8)	46 (12.8)	61 (12.9)
- mRS 5	83 (10.0)	43 (11.9)	40 (8.4)
- mRS 6	53 (6.4)	26 (7.2)	27 (5.7)
Adherent to (clinic) FU	487 (58.4)	238 (66.1)	249 (52.5)
Mean time of FU (months)	13.9 ± 13.2	18.0 ± 14.9	10.0 ± 9.8
Extensive neuropsychological test at FU	253 (30.3)	52 (14.4)	201 (42.4)
Cognitive diagnosis at follow up	157 (37.6)	93 (42.9)	64 (31.8)
- No cognitive impairment	261 (62.4)	124 (57.1)	137 (68.2)
- PSCI			
Neuropsychiatric symptoms at FU** (symptoms, n°)	2.5 ± 2.0	2.9 ± 2.1	2.3 ± 2.0
Depression at FU**	95 (43.6)	29 (59.2)	75 (44.4)
Anxiety at FU**	31 (14.2)	7 (14.3)	24 (14.3)

FLTD-CDR= Frontotemporal Lobar modified Clinical Dementia Rating; FU= Follow-up; IQCODE= Informant Questionnaire on Cognitive Decline in the Elderly; mRS= modified Rankin Scale; PSCI= Post-Stroke Cognitive Impairment; TIA= Transient Ischemic Attack.
Data are shown as mean±SD, or absolute and relative frequency.
* data available for 756 patients (324 patients in VAS-COG protocol 1.0 and 432 patients in VAS-COG protocol 2.0).
** data available for 218 patients.

NIHSS score at admission (9.5 ± 7.8 vs. 3.7 ± 4.1 $p < 0.001$), mRS at discharge (3.4 ± 2.0 vs. 1.4 ± 1.4, $p < 0.001$), NIHSS score at discharge (5.5 ± 6.5 vs. 1.5 ± 2.4, $p < 0.001$) and CDR sum of the boxes (4.9 ± 6.4 vs. 1.5 ± 3.0, $p < 0.001$).

Extensive neuropsychological testing at follow-up was implemented from 52/360 (14.4 %) patients in VAS-COG protocol 1.0 to 201/474 (42.4 %) patients in VAS-COG protocol 2.0: PSCI was detected in 124/217 (57.1 %) and 137/201 (68.2 %) patients, respectively.

Many outpatients were lost at follow-up during the period of the COVID-19 pandemic because of the temporary closure of outpatient clinics and for the fear of going to a hospital for non-life-saving reasons.

At follow-up, patients presented on average 2.5 neuropsychiatric symptoms on NPI-q, 95/218 (43.2 %) patients were found to have depressive symptoms on CES-D and 31/218 (14.2 %) anxiety symptoms on SAS; 35/95 (37 %) patients with a pathological score at CES-D have also a PSCI.

Eighty-five patients underwent a second extensive neuropsychological assessment at 18 months; in 63 patients (74.1 %) cognitive diagnosis was the same of the first neuropsychological assessment, 14 patients (16.5 %) had worse performances at 18 months than at 3/6 months from the cerebrovascular event (8 patients shifted from a normal cognition to a mild cognitive impairment and 6 patients from mild to a major cognitive impairment), while 8 patients improved from mild cognitive impairment to a normal cognition. Only ten patients have been so far tested at 36 months with results overlapping those obtained at the 18-month neuropsychological examination.

Discussion

Stroke is the third most common cause of disability worldwide and therefore, in addition, to acute phase strategies, stroke survivors require careful and thorough long-term care.

After 5 years of experience, this VAS-COG pathway appears to be a useful service to highlight psycho-cognitive issues related to stroke, whose characterization is relevant for clinicians and for patients and their caregivers. The early recognition of these problems meets the need of the family to understand the psycho-cognitive changes that occur after stroke and potentially allows them to receive adequate care and support [43]. Some of the good clinical practices suggested as anticipatory guidance are carried out in our outpatient clinic (i.e., management of stroke risk factors to prevent stroke recurrence and evaluation for comorbid complications) but it is certainly possible to implement them in the future.

The risk for cognitive impairment is increased by a history of stroke and is determined by a complex interplay of multiple factors including modifiable and non-modifiable risk factors, index stroke characteristics, and the overall brain health [44]. A mild or major pre-stroke cognitive impairment was found in 43 % of patients admitted to our stroke unit and a post-stroke cognitive impairment was detected in two-thirds of patients who were adherent to follow up.

To date, accuracy of informant tests for diagnosis of pre-stroke cognitive decline has not been investigated and quantification of patients with pre-stroke varies depending on the scale used: in our cohort IQCODE with a cut-off of 3.3 identified a pre-stroke cognitive impairment in 35.4 % of patients, while using FLTD-CDR 43.3 % patients had a score ≥0.5 (corresponding to a cut-off to detect at least a mild cognitive disorder) and 19.4 % had a score ≥1 (corresponding to a cut-off for major cognitive disorder).

The use of a comprehensive cognitive battery (VAS-COG protocol 1.0) increases the possibility of identifying minor cognitive disorders at follow up compared with history collection with a caregiver and cognitive screening tests administered during a neurological outpatient clinic (VAS-COG protocol 2.0).

PSCI rate in previous studies massively varies (from 4 to over 70 %) as a consequence of stroke subtypes enrolled, of characteristics of the study population, of the timing of diagnosis of PSCI, and of the criteria used to detect PSCI [45–47].

However, it should be emphasized that the true prevalence of PSCI in our cohort cannot be calculated due to the large number of drop out; it must be considered that our dropout patients are those who had more severe neurological outcomes [10]; therefore, the proportion of patients with neuropsychological consequences after stroke is likely underestimated. Practical benefits of our stroke care pathway are the possibility for patients of receiving a formal diagnosis of post-stroke cognitive impairment and the recognition of civil disability and possible accompanying allowance.

All individuals who have experienced a stroke are at a high risk of post-stroke depression due to a dysfunction of neurotransmission due to ischemic/hemorrhagic lesions and neuroinflammation.

Nearly half of patients of our cohort experienced depression

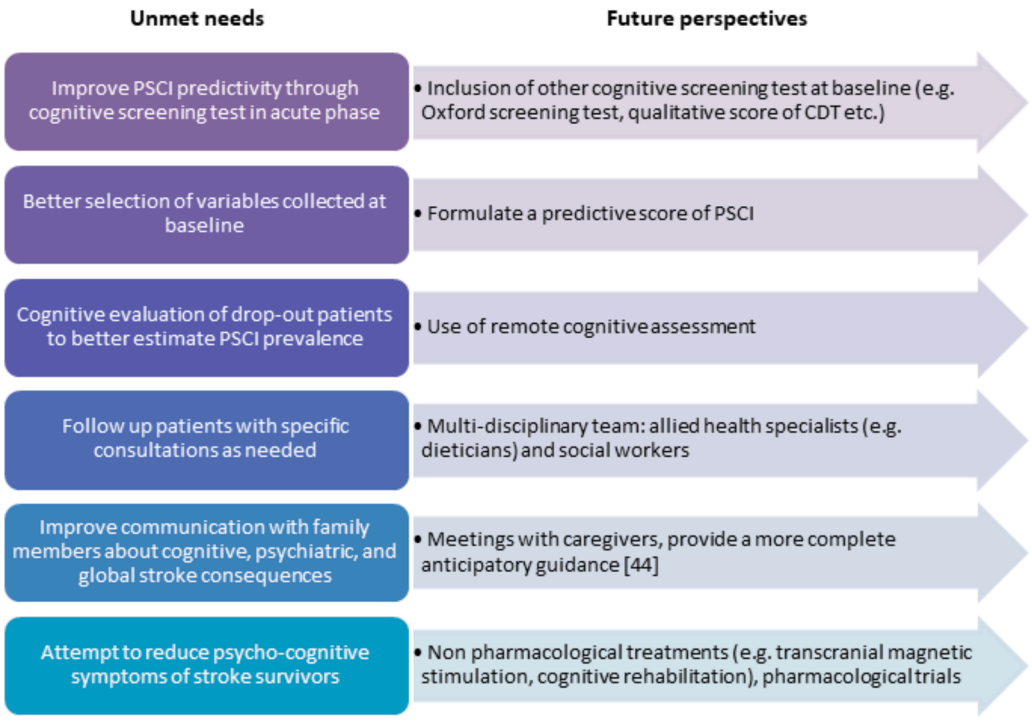

Fig. 3. Unmet needs and future perspectives.
List of abbreviations CDT=clock drawing test; PSCI=post-stroke cognitive impairment.

symptoms after the event and required a pharmacological treatment that was prescribed during follow-up visits by the referring neurologist. We cannot currently offer psychotherapy in our hospital. When necessary, patients were sent for psychiatric evaluation.

Post-stroke depression prevalence has previously been reported in 20–60 % among stroke survivors [48] and our data confirm its high frequency. One-third of patients who presented with depression at follow-up in the VAS-COG protocol 2.0 were also found to have PSCI; it cannot be ruled out that some of these patients may have cognitive deficits secondary to depression.

In addition to the possibility to highlight neuropsychiatric disorders in stroke survivors, the VAS-COG stroke care pathway allows the collection of many clinical information that can be useful for research purposes.

All the variables collected were initially included because they were potentially useful for performing analyses; probably not all of the blood tests we report are useful; moreover, we have used 3 different scales to assess white matter lesions, while one is likely sufficient.

Implementation with an extensive neuropsychological evaluation in the follow up allowed to increase the detection of cognitive deficits in stroke patients; milder cognitive impairments probably elude detection during "classical" neurological outpatients clinic, particularly in individuals with higher baseline intellectual ability. Our experience testifies that a team neuropsychologists may improve the quality of such a service.

The findings reported in this study should be considered in the context of one main limitation, i.e., a high dropout rate, mainly due to the high mortality and morbidity rates of cerebrovascular diseases. Moreover, another current limitation of this pathway is a certain shortage of specific therapeutic interventions, either pharmacological or non-pharmacological.

Considering the lack of pharmacological therapy, non-pharmacological approaches to treatment of the cognitive sequelae of stroke could be useful. Limitations in the use of such therapies are twofold: their efficacy has not yet been adequately proven in this population and the national health systems still do not support these services with adequate resources.

In Fig. 3, we reported unmet needs and future perspectives of our stroke care pathway.

In conclusion, we propose our VAS-COG stroke care pathway as a model to follow up stroke patients because of the frequent cognitive and behavioural consequences which are still neglected by daily neurological practice. Extension of this model to other centers would allow the enrolment of larger cohorts in which pharmacological studies could be conducted with the aim of slowing down the onset or the progression of psycho-cognitive disorders.

Ethics approval and consent to participate

The procedures were carried out in accordance with the Declaration of Helsinki. All patients signed an informed consent to undergo any assessment needed in clinical practice, including neuroimaging. The local IRB subsequently granted approval for the retrospective analysis of the data.

CRediT authorship contribution statement

I. Cova: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **F. Mele:** Writing – review & editing, Software, Data curation. **A. Nicotra:** Writing – review & editing, Software, Methodology, Data curation. **G. Maestri:** Writing – review & editing, Methodology, Data curation. **V. Cucumo:** Writing – review & editing, Data curation. **S. Pomati:** Writing – review & editing, Methodology. **E. Salvadori:** Writing – review & editing, Supervision, Software, Methodology. **L. Pantoni:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

LP is member of the editorial boards of Neurology, Cerebrovascular Diseases, European Stroke Journal, Cerebral Circulation—Cognition and Behaviour and associate editor of Neurological Sciences.

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