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Applicability and Correlates of a Symptom-Led Staging System for Primary Progressive Aphasia

Edoardo Nicolò Aiello[1] | Arianna Moreschi[1] | Valeria Crispiatico[2] | Beatrice Curti[1] | Giulia De Luca[1] | Monica Lazzarini[3] | Alessio Maranzano[1] | Vincenzo Silani[1,4] | Nicola Ticozzi[1,4] | Stefano Francesco Cappa[1] | Federico Verde[1] | Barbara Poletti[1,5]

[1]Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, Milano, Italy | [2]Department of Psychology, University of Milano-Bicocca, Milano, Italy | [3]Department of Biomedical and Clinical Sciences "Luigi Sacco", Università Degli Studi di Milano, Milano, Italy | [4]Department of Pathophysiology and Transplantation, "Dino Ferrari" Center, Università Degli Studi di Milano, Milano, Italy | [5]Department of Oncology and Hemato-Oncology, Università Degli Studi di Milano, Milano, Italy

Correspondence: Barbara Poletti (b.poletti@auxologico.it)

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ABSTRACT

Background: This study aimed at assessing the applicability of a symptom-led staging system for primary progressive aphasia (PPA) based on retrospective medical records, as well as at exploring their demographic and clinical correlates.

Methods: 75 PPA patients (10 semantic, 28 non-fluent, 22 logopenic, and 16 mixed variants) were retrospectively staged according to the PPA Progression Planning Aid (PPA-Squared) system, which stages the disease by accounting for clinical features along three axes: (1) Communication; (2) Non-Verbal Thinking and Personality; (3) Personal Care and Well-Being. The percentage of successfully staged patients was computed. The association between PPA-Squared scores and demographic and clinical data was tested via non-parametric tests. The predictive capability of PPA-Squared scores towards survival was explored via a Mantel-Cox test.

Results: 89.3% of patients were successfully staged based on retrospective medical records. The PPA-Squared was associated with the MMSE ($p < 0.001$), ADL ($p = 0.021$), and IADL scores ($p < 0.001$) and a set of second-level cognitive measures tapping on attention, executive functions, language, long-term memory, and visuo-spatial abilities ($p \leq 0.049$). No association was found between the PPA-Squared and demographic features, symptom duration, PPA phenotype, the presence of motor involvement, and survival.

Discussion: The PPA-Squared is a feasible and clinically valid tool for staging PPA patients based on their cognitive and functional *status*.

1 | Background

Primary progressive aphasia (PPA) is an adult-onset, language-led dementing condition [1] whose natural history and thus prognosis, due to its phenotypic heterogeneity, is yet to be fully understood [2]. This, together with the need for informed and tailored management plans, as well as with that of monitoring the effectiveness of available both pharmacological and non-pharmacological treatments, makes it advisable to employ staging systems specific to such a disorder [3, 4]. In this framework, a staging system based on caregivers' reports on patients' signs and symptoms has been recently proposed—i.e., the PPA

Edoardo Nicolò Aiello and Arianna Moreschi shared first authorship.

Federico Verde and Barbara Poletti shared last authorship.

Progression Planning Aid (PPA-Squared) [5, 6]. This system, addressing each of the three main PPA variants—i.e., semantic (svPPA), non-fluent (nfvPPA), and logopenic (lvPPA) –, stages the disease by accounting for clinical features along three axes: (1) communicative skills (Communication); (2) extra-linguistic cognitive efficiency and behavior (Non-Verbal Thinking and Personality, NVTP); (3) functional independence (Personal Care and Well-Being, PCWB) [5, 6]. As its development has relied on a large number of caregiver-reported, multi-dimensional symptoms, the PPA-Squared is thought to outperform, in terms of comprehensiveness, previous staging systems [5, 6]. Nevertheless, in spite of its promising features, no study to date has provided evidence on the applicability and correlates of the PPA-Squared in clinical settings.

Given the above premises, the current study aimed at assessing the applicability of the PPA-Squared on the basis on retrospective medical records, as well as at exploring its demographic and clinical correlates, within a single-center, naturalistic cohort of PPA patients.

2 | Methods

2.1 | Participants

Data on 75 in- and out-patients consecutively referred to the Department of Neurology of IRCCS Istituto Auxologico, Milano, Italy between 2002 and 2025 and being diagnosed with PPA were retrospectively retrieved. For those diagnosed with PPA in the context of either frontotemporal lobar degeneration (FTLD) or Alzheimer's disease (AD) prior to the delivery of Gorno-Tempini et al.'s [1] diagnostic criteria, medical records were reviewed in order to classify them in accordance with such a nosographic system. Patients with PPA due to AD that presented with features of both lvPPA and either svPPA or nfvPPA (e.g., phonological and lexical deficits along with evidence of semantic or morpho-syntactic impairment, respectively) were classified as mixed PPA (mPPA) [7]. Remaining patients were classified as imaging-supported either nfvPPA, svPPA or lvPPA according to Gorno-Tempini et al.'s [1] nosographic system. All patients were Italian native-speakers.

2.2 | Materials

2.2.1 | PPA-Squared

Patients were staged according to the PPA-Squared scales designed for nfvPPA, svPPA [5] and lvPPA [6] based on retrospective medical records. To the aim of this study, we considered the clinical documentation covering the hospitalization period for patients being diagnosed in an inpatient setting, whilst for those attending the outpatient clinic, the visit where the diagnosis was established.

Each PPA-Squared scale identifies six disease stages, with 1 being "Very mild" and 6 "Profound". Symptoms attaining the Communication axis are represented within each of the six stages of each version of the PPA-Squared. By contrast, those belonging to the NVTP and PCWB axes are distributed as follows: (1) NVTP symptoms are represented from Stage 1 to Stage 4 within the PPA-Squared-svPPA and -lvPPA and from Stage 1 to Stage 5 within the PPA-Squared-nfvPPA; (2) PCWB symptoms are represented from Stage 2 onwards within the PPA-Squared-nfvPPA and -svPPA and from Stage 4 onwards within the PPA-Squared-lvPPA. A given stage was reached whenever at least one related symptom—regardless of the axis to which it belongs—could be traced within available clinical records. Otherwise said, we assigned an overall PPA-Squared stage score based on the most severe symptom on any axis.

Patients with mPPA were staged both via the PPA-Squared for lvPPA [6] and that for either svPPA or nfvPPA [5]—due to the unavailability of a version of the scale that is specific to such a phenotype. For these patients, the mean between the stages yielded by the two versions was taken into account for analytical purposes—with decimal values being rounded up to the nearest integer. For instance, an mPPA patient being classified as Stage 2 by the PPA-Squared-lvPPA and as Stage 3 by the PPA-Squared-svPPA was eventually classified as Stage 3, that is, $(2+3)/2=2.5\rightarrow 3$.

2.2.2 | Demographic and Clinical Measures

Besides sex and education, the following data were retrieved: (1) age at diagnosis; (2) symptom duration (in months) at diagnosis; (3) survival at March 23rd, 2025; (4) co-morbid motor neuron disease (MND); (5) co-morbid extra-pyramidal disorders (EPDs); (6) Mini-Mental State Examination (MMSE) [8] scores; (7) scores on a second-level cognitive battery including measures of attention, executive functioning, short- and long-term memory, language, and constructional praxis (Table 1) [9–18]; (8) Activities of Daily Living (ADL) [19] and Instrumental Activities of Daily Living (IADL) [20] scores. Diagnoses of co-morbid MND were established by a neurologist in accordance with El Escorial criteria [21]; EPDs were likewise diagnosed by a neurologist by relying on an in-depth neurological examination.

The second-level cognitive measures herewith taken into account were drawn from the battery that is employed at our Center for the diagnostic work-up of patients with cognitive complaints. This battery includes a set of core tests sampling the main cognitive domains/functions and has not received specific validation in PPA patients.

2.3 | Statistics

The applicability of the PPA-Squared was assessed, in terms of proportions of successfully staged patients, both within the whole cohort and separately within the following sub-cohorts—defined on the basis of the availability of a given set of clinical information: (1) patients with both a neurological and a neuropsychological assessment; (2) patients with a neurological assessment only, being however comprehensive of the MMSE; (3) patients with a neurological assessment only, however lacking the MMSE.

Due to their semi-continuous nature, non-parametric tests were run for assessing the correlates of PPA-Squared scores. More specifically, the association between PPA-Squared scores and continuous demographic and clinical measures (i.e., age, education,

TABLE 1 | Patients' demographic and clinical measures.

	svPPA	nfvPPA	lvPPA	mPPA	*p*
N	10	27	22	16	
Age (years)	72.8 ± 6.3 (62–80)	69.81 ± 8.99 (52–88)	74.95 ± 8.82 (55–86)	76.5 ± 4.93 (68–84)	0.038[g]
Sex (M/F, %)	5/5 [50%/50%]	21/6 [77.8%/22.2%]	9/13 [40.9%/59.1%]	8/8 [50%/50%]	0.055[h]
Education (years)[a]	13 ± 2.1 (11–17)	10.5 ± 4.59 (4–21)	11.84 ± 3.72 (8–17)	10.75 ± 4.41 (5–17)	0.536[g]
Symptom duration (months)[b]	40.11 ± 38.65 (9–124)	37.85 ± 39.54 (4–216)	56.43 ± 55.28 (12–272)	35.87 ± 19.54 (11–82)	0.282[g]
Survival (death, %)[c]	4 [40%]	18 [81.8%]	7 [35%]	4 [26.7%]	0.002[h]
Motor neuron disease (%)	—	4 [14.8%]	—	—	0.055[h]
Extra-pyramidalism (%)	—	4 [14.8%]	—	—	0.057[h]
PPA-squared[d]					—
Stage 1	—	—	1 [5.6%]	—	
Stage 2	1 [10%]	1 [4%]	—	1 [7.1%]	
Stage 3	4 [40%]	8 [32%]	6 [33.3%]	3 [21.4%]	
Stage 4	2 [20%]	7 [28%]	5 [27.8%]	7 [50%]	
Stage 5	3 [30%]	4 [16%]	5 [27.8%]	3 [21.4%]	
Stage 6	—	5 [20%]	1 [5.6%]	—	
MMSE[e]	23 ± 6.16 (13–28)	19 ± 8.54 (1–27)	18.83 ± 7.07 (4–27)	18.79 ± 6.2 (8–28)	0.585[g]
Functional independence[f]					
ADL*	97.22 ± 6.8 (83.33–100)	70.83 ± 39.38 (16.67–100)	91.67 ± 17.82 (50–100)	92.86 ± 18.9 (50–100)	0.489[g]
IADL*	65.42 ± 30.18 (20–100)	45 ± 38.94 (0–80.00)	79.79 ± 25.04 (33.33–100)	75.56 ± 25.22 (20–87.5)	0.146[g]

Abbreviations: BADL = Activities of Daily Living, IADL = Instrumental Activities of Daily Living, lv = logopenic variant, m = mixed, MMSE = Mini-Mental State Examination, nfv = non-fluent variant, PPA = primary progressive aphasia, PPA-Squared = Primary Progressive Aphasia Progression Planning Aid, sv = semantic variant.

[a]Data available for $N = 6$ patients with svPPA, $N = 22$ patients with nfvPPA, $N = 19$ patients with lvPPA.

[b]Data available for $N = 9$ patients with svPPA, $N = 21$ patients with lvPPA, $N = 15$ patients with mPPA.

[c]Data available for $N = 22$ patients with nfvPPA, $N = 20$ patients with lvPPA, $N = 15$ patients with mPPA.

[d]Data available for $N = 25$ patients with nfvPPA, $N = 18$ patients with lvPPA, $N = 14$ patients with mPPA.

[e]Data available for $N = 5$ patients with svPPA, $N = 15$ patients with nfvPPA, $N = 18$ patients with lvPPA, $N = 14$ patients with mPPA.

[f]Data available for $N = 6$ patients with svPPA, $N = 4$ patients with nfvPPA, $N = 8$ patients with lvPPA, $N = 7$ patients with mPPA.

[g]Kruskall-Wallis' *H*-statistic.

[h]χ^2-statistic. Categorical variables are reported as frequencies and, in brackets, percentages. Continuous variables are reported as $M \pm SD$ and, in brackets, *range*.

*Expressed as percentage out of the applicable total.

symptom duration, MMSE scores, ADL/IADL scores and second-level cognitive scores) was tested via Spearman's coefficients. At variance, the association between PPA-Squared scores and categorical demographic and clinical measures (i.e., sex, phenotype—nfvPPA vs. svPPA vs. lvPPA vs. mPPA –, presence vs. absence of MND/EPD) was tested via Mann–Whitney/Kruskall Wallis tests that addressed PPA-Squared scores as the outcome.

Finally, the discrepancy in survival curves between different PPA-Squared stages was tested via a Mantel-Cox test (with time being computed as the number of months elapsed between onset and the aforementioned index date, that is, March 23rd, 2025).

Analyses were run via IBM SPSS Statistics 29 (IBM Corp., 2023) and jamovi 2.3 (the jamovi project, 2022). Missing data were excluded pairwise.

3 | Results

3.1 | Applicability of the PPA-Squared

A summary of patients' demographic and clinical features is reported in Table 1, whilst patients' second-level cognitive measures are reported in Table 2.

As to the availability of clinical records, 43 patients (57.33%) underwent both a neuropsychological and a neurological assessment, 14 patients (18.67%) had a neurological report inclusive of an MMSE score, and 18 patients (24%) underwent a neurological assessment without the MMSE being administered. Within the whole cohort, 8 patients (two with nfvPPA, four with lvPPA, and two with mPPA) could not be successfully staged due to the unavailability of information regarding the NVTP ($N=2$) and/or the PCWB axis ($N=7$), thus resulting in an overall applicability rate of the PPA-Squared of 89.3%. When looking at individual sub-cohorts, the applicability rate was 95.3% for patients with both a neurological and neuropsychological assessment (2 patients out of 43 that could not be staged), 64.3% for those with a neurological assessment inclusive of the MMSE and (5 patients out of 14 that could not be staged), and 94.4% for those with a neurological assessment lacking an MMSE score (1 patient out of 18 could not be staged).

3.2 | Correlates of the PPA-Squared

PPA-Squared scores were unrelated to sex ($U=502.5$; $p=0.570$), age ($r_s(67)=0.11$; $p=0.369$), education ($r_s(56)=0.09$; $p=0.509$) and symptom duration ($r_s(64)=0.11$; $p=0.398$); moreover, these scores were homogeneously distributed across different phenotypes ($\chi^2(3)=1.03$; $p=0.794$). No association between PPA-Squared scores and the co-occurrence of motor involvement—i.e., MND or EPD—was detected ($U=197.5$; $p=0.445$).

Significant, negative associations were detected between PPA-Squared stages and both the MMSE ($r_s(46)=-0.66$; $p<0.001$) (Figure 1) and the vast majority of second-level cognitive scores (Table 3) tapping on attention, executive functions, language, long-term memory and visuo-spatial abilities. As to measures of functional independence, both ADL ($r_s(25)=-0.46$; $p=0.021$) and IADL scores ($r_s(25)=-0.68$; $p<0.001$) proved to be negatively associated with the PPA-Squared.

The Mantel-Cox test was run on $N=56$ patients, that is, those with complete information on symptom duration and survival *status*; additionally, the sole patient out of the whole cohort being assigned a PPA-Squared score of 1 was left out of this analysis in order for the model to converge. No discrepancies in survival curves as a function of different PPA-Squared stages were detected ($\chi^2(4)=3.15$; $p=0.532$) (Figure S1).

4 | Discussion

This study supports the applicability of the PPA-Squared as a staging tool for patients with different PPA phenotypes, also providing evidence on its association with clinical measures—namely, cognitive scores and measures of functional independence.

The vast majority of patients (~89%) were successfully staged on the sole basis of retrospective medical records. Hence, it is reasonable to assume that the PPA-Squared would be likewise readily applicable within prospective both clinical and experimental scenarios. Relatedly, it is noteworthy that patients herewith proved to be successfully staged even in the absence of a neuropsychological report. This suggests that the PPA-Squared might be effortlessly applied even within the context of a neurological examination—provided that information on cognitive and behavioral history be also mindfully collected by the practitioner from both patients' and proxies' perspectives. In this respect, it is noteworthy that the lower rate of applicability was found in patients with a neurological examination not inclusive of the MMSE. This is theoretically unexpected—given that, although unsuitable for assessing PPA patients, the MMSE still might provide some additional information through standardized tasks. A tentative explanation for such a finding might lie in the fact that administering the MMSE might subtract time from a more detailed inquiry on patients' cognitive and behavioral history, this possibly resulting in clinicians not being able to collect a given set of information that is crucial for staging patients according to the PPA-Squared.

As to the correlates of the PPA-Squared, no association was detected with demographic features—this suggesting that the application of such a staging system is not likely to be confounded by patients' age, sex and educational level. Moreover, no differences in the distribution of PPA-Squared scores were found across the four phenotypes—this hinting at the fact that this tool homogeneously captures PPA progression regardless of the discrepancies in stage allotment as *per* each phenotype-specific scale. In addition, the significant associations herewith yielded between PPA-Squared scores and both the MMSE and a set of second-level cognitive measures, as well as with measures of everyday-life independence, support the notion that this tool represents a valid estimate of cognition and function in PPA patients. Interestingly, in this respect, the lack of a significant correlation between the PPA-Squared and symptom duration hints at the fact that this staging system captures PPA severity—in terms of cognitive involvement and reduced functional independence—regardless of how long the disease has been lasting. A further finding that deserves consideration lies in the absence of associations between motor involvement (i.e., MND or EPD) and PPA-Squared scores. Such a result is likely to be accounted for by the fact that PPA patients with co-occurrent MND/EPD often present with motor involvement early in the disease course [22, 23] – this possibly impacting on patients' disease trajectories in unexpected ways [2]. Finally, the fact that PPA-Squared scores herewith proved to be uninformative towards patients' survival appears to be consistent with the original scopes of this staging system, which has been developed to plan patients' clinical management by tailoring interventions in accordance with their clinical features and needs, whilst not to predict their survival [5, 6].

4.1 | Limitations and Future Perspectives

This report has the merit of providing evidence that supports the applicability and validity of the PPA-Squared in a fairly large patient cohort, representative of different PPA phenotypes, and characterized at clinical, cognitive, and functional levels. With that being said, the present study is of course not devoid of limitations.

First, as already mentioned, its reliance on retrospective data undoubtedly limited the applicability rate of the system itself;

TABLE 2 | Patients' second level cognitive scores.

	svPPA	nfvPPA	lvPPA	mPPA	p^o
Attention					
Digit Cancelation Test[a]	29 ± 5.66 (25–33)	38.33 ± 13.79 (9–56)	29 ± 11.94 (12–43)	35.8 ± 16.12 (10–49)	0.270
Trail-Making Test-A[b]	75.75 ± 32.92 (36–104)	140.07 ± 124.46 (42–438)	95.4 ± 71.81 (49–296)	150.22 ± 90.18 (44–337)	0.257
Trail-Making Test-B[c]	251.67 ± 193.712 (104–471)	304.11 ± 131.37 (98–494)	424 ± 218.46 (257–840)	306.50 ± 243.95 (134–479)	0.548
Trail-Making Test-B-A[c]	171.67 ± 172.67 (68–371)	231.44 ± 107.52 (56–391)	354.5 ± 212.16 (182–763)	239 ± 210.72 (90–388)	0.551
Executive functions					
Frontal Assessment Battery[d]	14.67 ± 0.58 (14–15)	10.33 ± 4.06 (4–16)	11 ± 2.14 (9–16)	10.88 ± 3.44 (7–16)	0.294
RCPM[e]	25.5 ± 2.65 (23–29)	23.07 ± 8.41 (4–33)	20.57 ± 5.88 (15–28)	19.43 ± 5.71 (10–26)	0.280
Phonemic Verbal Fluency[f]	18.75 ± 12.29 (5–31)	8.54 ± 6.69 (0–21)	13.75 ± 8.17 (3–29)	10.20 ± 10.06 (0–34)	0.273
Language					
Token Test[g]	—	23.96 ± 8.07 (12–34)	21.31 ± 10.58 (0–34.5)	22.07 ± 6.77 (15–33)	0.793
Boston Naming Test[h]	12.5 ± 0.71 (12–13)	25.83 ± 14.87 (2–50)	19 ± 20.08 (0–40)	37 ± 4.24 (34–40)	0.315
Semantic Verbal Fluency[i]	12 ± 7.53 (1–18)	14.43 ± 10.97 (2–32)	16.38 ± 7.41 (5–25)	9.3 ± 6.26 (0–22)	0.349
Memory					
Forward Digit Span[j]	5.75 ± 1.26 (4–7)	3.47 ± 1.3 (0–6)	3.7 ± 1.49 (0–5)	4.5 ± 1.08 (3–6)	0.019
Forward Corsi Span[k]	5.33 ± 1.16 (4–6)	2.64 ± 2.24 (0–6)	3.64 ± 1.36 (0–5)	2.8 ± 2.1 (0–6)	0.132
Babcock Memory Test[l]	4 ± 3.91 (1.5–8.5)	5.28 ± 3.21 (0.5–10.5)	4.3 ± 3.4 (1.5–9.5)	2.69 ± 3.67 (0–11)	0.357
Praxis and VS abilities					
Clock Drawing Test[m]	2.25 ± 3.18 (0–4.5)	4.63 ± 4.17 (0–10)	4.00 ± 2.63 (0–6.5)	3.27 ± 2.42 (0–7)	0.833
Design Copy[n]	13.33 ± 1.16 (12–14)	11.00 ± 2.83 (6–14)	11.5 ± 1.23 (10–13)	9.4 ± 5.9 (2–14)	0.475

Note: Continuous variables are reported as $M \pm SD$ and, in brackets, *range*.
Abbreviations: lv = logopenic variant, m = mixed, nfv = non-fluent variant, PPA = primary progressive aphasia, RCPM = Raven's Colored Progressive Matrices, sv = semantic variant.
[a]Data available for $N = 2$ patients with svPPA, $N = 15$ patients with nfvPPA, $N = 7$ patients with lvPPA, $N = 5$ patients with mPPA.
[b]Data available for $N = 4$ patients with svPPA, $N = 15$ patients with nfvPPA, $N = 10$ patients with lvPPA, $N = 9$ patients with mPPA.
[c]Data available for $N = 3$ patients with svPPA, $N = 9$ patients with nfvPPA, $N = 6$ patients with lvPPA, $N = 2$ patients with mPPA.
[d]Data available for $N = 3$ patients with svPPA, $N = 9$ patients with nfvPPA, $N = 8$ patients with lvPPA, $N = 8$ patients with mPPA.
[e]Data available for $N = 4$ patients with svPPA, $N = 15$ patients with nfvPPA, $N = 7$ patients with lvPPA, $N = 7$ patients with mPPA.
[f]Data available for $N = 4$ patients with svPPA, $N = 13$ patients with nfvPPA, $N = 8$ patients with lvPPA, $N = 10$ patients with mPPA.
[g]Data available for $N = 0$ patients with svPPA, $N = 14$ patients with nfvPPA, $N = 8$ patients with lvPPA, $N = 7$ patients with mPPA.
[h]Data available for $N = 2$ patients with svPPA, $N = 12$ patients with nfvPPA, $N = 3$ patients with lvPPA, $N = 2$ patients with mPPA.
[i]Data available for $N = 4$ patients with svPPA, $N = 14$ patients with nfvPPA, $N = 8$ patients with lvPPA, $N = 10$ patients with mPPA.
[j]Data available for $N = 4$ patients with svPPA, $N = 15$ patients with nfvPPA, $N = 10$ patients with lvPPA, $N = 10$ patients with mPPA.
[k]Data available for $N = 3$ patients with svPPA, $N = 14$ patients with nfvPPA, $N = 11$ patients with lvPPA, $N = 10$ patients with mPPA.
[l]Data available for $N = 3$ patients with svPPA, $N = 9$ patients with nfvPPA, $N = 5$ patients with lvPPA, $N = 8$ patients with mPPA.
[m]Data available for $N = 2$ patients with svPPA, $N = 15$ patients with nfvPPA, $N = 8$ patients with lvPPA, $N = 11$ patients with mPPA.
[n]Data available for $N = 3$ patients with svPPA, $N = 13$ patients with nfvPPA, $N = 6$ patients with lvPPA, $N = 5$ patients with mPPA.
[o]Kruskall-Wallis' H-statistic.

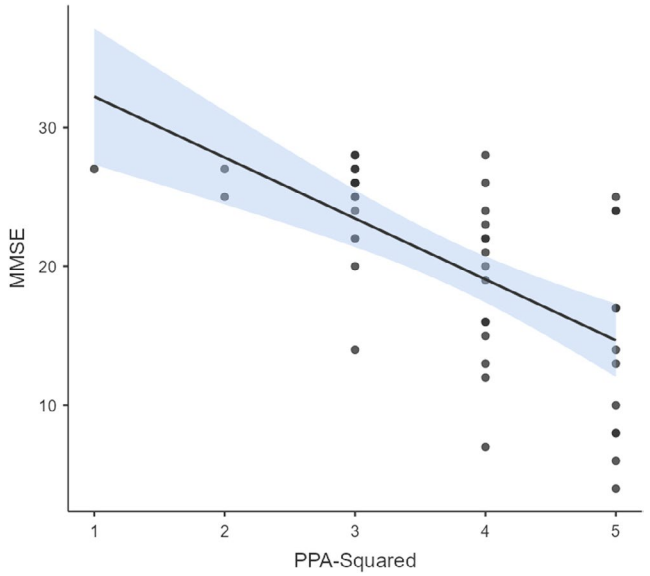

FIGURE 1 | Scatterplot for the association between PPA-Squared stages and the MMSE. MMSE = Mini-Mental State Examination, PPA-squared = primary progressive aphasia progression planning aid.

TABLE 3 | Correlation coefficients between PPA-Squared stages and second-level cognitive scores.

Measure	*N*	r_s	*p*
Attention			
Digit Cancelation test	29	−0.48	0.008
Trail-Making Test-A	36	0.50	0.002
Trail-Making Test-B	19	0.30	0.218
Trail-Making Test-B-A	19	0.26	0.291
Executive functions			
Frontal Assessment Battery	26	−0.36	0.070
Raven's Colored Progressive Matrices	32	−0.47	0.006
Phonemic Verbal Fluency	33	−0.55	0.001
Language			
Token Test	27	−0.49	0.010
Boston Naming Test	19	−0.50	0.049
Semantic Verbal Fluency	34	−0.42	0.013
Memory			
Forward Digit Span	38	−0.11	0.509
Forward Corsi Span	37	−0.49	0.002
Babcock Memory Test	24	−0.46	0.023
Praxis and visuo-spatial abilities			
Constructional Apraxia Test	26	−0.29	0.151
Clock Drawing Test	34	−0.57	< 0.001

Abbreviation: PPA-squared = primary progressive aphasia progression planning aid.

hence, it is strongly advised that future investigations focus on applying the PPA-Squared in a prospective fashion. This issue applies even more to those variables that suffer from recall biases—namely, symptom duration and survival, which both rely on the time of onset estimated by patients' caregivers. Hence, one cannot rule out that this accounted, at least to some extent, for the lack of association between PPA-Squared scores and both symptom duration and survival herewith detected. Relatedly, the retrospective nature of this study resulted in a number of missing values for several variables—this possibly limiting the generalizability of the present findings, by also preventing us from an in-depth characterization of some clinical features. This last issue particularly applies to the description of patients' pyramidal and extra-pyramidal involvement, which has been herewith reported in a dichotomic fashion: it would be thus advisable for future investigations to inspect the association between the motor axis of the PPA-Squared (i.e., the PCWB) and standardized, semi-continuous/continuous measures of both pyramidal (e.g., the ALS Functional Rating Scale-Revised [24]) and extra-pyramidal (i.e., the third section of the Movement Disorders Society—Unified Parkinson's Disease Rating Scale [25]) involvement—especially given that PPA patients might present with motor signs/symptoms that would not qualify for an additional motor diagnosis [4, 22, 23].

An additional element deserving consideration lies in the scoring approach herewith employed for the PPA-Squared—with patients being assigned a given stage based on the most severe symptom on any axis. In fact, whilst this system has been originally thought to both stage patients along its three separate axes (i.e., Communication, NVTP and PCWB) and to produce an overall, composite staging score [5, 6], no clear guidance has been provided yet on which might be the most clinically appropriate algorithm to assign such a global score. The approach herewith embraced is likely to suffer from the fact that the degree of severity along an individual axis might carry the overall staging score assigned, thus possibly under- or over-estimating patients' actual conditions. Noteworthily, such an issue affects to an even greater extent mPPA patients, given that no version of the staging system has been developed for these atypical—albeit frequently observed [4]—syndromes. It would be thus advisable for future studies to compare the effectiveness of different PPA-Squared scoring algorithms in capturing patients' clinical characteristics, with particular attention being given to atypical phenotypes.

Furthermore, this study addressed PPA-nonspecific cognitive measures by nevertheless not including standardized language batteries specifically designed to assess PPA patients: hence, it would be fruitful for future investigations to focus on the association between the PPA-Squared and such instruments—such as the Screening for Aphasia in NeuroDegeneration (SAND) [26] and the Mini-Linguistic State Examination (MLSE) [27]. In this respect, it would also be relevant for further studies to comparatively assess the degree of association between PPA-nonspecific (e.g., the cognitive battery herewith addressed) and PPA-specific (e.g., the SAND or the MLSE) measures on one hand, and the PPA-Squared on the other, in order to determine whether this staging system actually captures meaningful, disease-specific information on patients' core clinical characteristics.

Two further topics deserve a mention as to future research on the topic. First, it would be relevant to test the ability of the PPA-Squared to stage PPA patients across different countries, and thus languages and cultures. Such an investigation would be of major importance especially in the light of recent cross-linguistic evidence suggesting that PPA phenotypes might differ on the basis of the language spoken [28, 29]. Demonstrating that the PPA-Squared is effective in capturing patients' *status* across different languages and cultures would in turn promote its employment within international both observational and interventional studies. Second, whilst the PPA-Squared has been originally developed within the context of a specialized referral center, further evidence is needed on its applicability within non-specialized clinical settings—such as primary care services and general memory clinics.

In conclusion, the present study suggests that the PPA-Squared is a feasible and clinically valid tool for staging PPA patients based on their cognitive and functional *status*, useful in both clinical and research settings.

Author Contributions

Edoardo Nicolo Aiello: conceptualization, analyses, drafting, revision; **Arianna Moreschi:** data curation, analyses, drafting, revision; **Valeria Crispiatico:** resources, revision; **Beatrice Curti, Giulia De Luca:** analyses, drafting, revision; **Alessio Maranzano:** data collection, revision; **Vincenzo Silani, Nicola Ticozzi, Stefano Francesco Cappa:** resources, revision; **Federico Verde:** data collection, resources, drafting, revision; **Barbara Poletti:** resources, revision, writing – review and editing.

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Ethics Statement

This study was approved by the Ethics Committee of IRCCS Istituto Auxologico Italiano (I.D.: 23C125).

Consent

Participants provided informed consent.

Conflicts of Interest

V. S. received compensation for consulting services and/or speaking activities from AveXis, Cytokinetics, Italfarmaco, Liquidweb S.r.l., and Novartis Pharma AG, receives or has received research supports from the Italian Ministry of Health, AriSLA, and E-Rare Joint Transnational Call. He is on the Editorial Board of *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, *European Neurology*, *American Journal of Neurodegenerative Diseases*, *Frontiers in Neurology*. B.P. received compensation for consulting services and/or speaking activities from Liquidweb S.r.l. B.P. is Associate Editor for *Frontier in Neuroscience*. N.T. received compensation for consulting services and/or speaking fees from Amylyx Pharmaceuticals, Biogen, Italfarmaco, and Zambon Biotech SA. He is Associate Editor for *Frontiers in Aging Neuroscience*. F.V. is Associated Editor for *Journal of Alzheimer's Disease*. E.N.A. serves as an Editorial Board Member for *BMC Neurology*. The other authors have nothing to declare.

Data Availability Statement

Datasets associated with the present study cannot be made publicly available on ethical-legal grounds but have been stored on an online repository (https://doi.org/10.5281/zenodo.17967871) and can be made available upon reasonable request of interested researchers to the Corresponding Author(s), who will forward a request for a data transfer agreement to the relevant Ethical Committee(s).

References

1. M. L. Gorno-Tempini, A. E. Hillis, S. Weintraub, et al., "Classification of Primary Progressive Aphasia and Its Variants," *Neurology* 76 (2011): 1006–1014.

2. H. Ulugut, S. Stek, L. E. Wagemans, et al., "The Natural History of Primary Progressive Aphasia: Beyond Aphasia," *Journal of Neurology* 269 (2022): 1375–1385.

3. C. R. Marshall, C. J. Hardy, A. Volkmer, et al., "Primary Progressive Aphasia: A Clinical Approach," *Journal of Neurology* 265 (2018): 1474–1490.

4. C. R. Belder, C. R. Marshall, J. Jiang, et al., "Primary Progressive Aphasia: Six Questions in Search of an Answer," *Journal of Neurology* 271 (2024): 1028–1046.

5. C. J. Hardy, C. Taylor-Rubin, B. Taylor, et al., "Symptom-Led Staging for Semantic and Non-Fluent/Agrammatic Variants of Primary Progressive Aphasia," *Alzheimer's & Dementia* 20 (2024): 195–210.

6. C. J. Hardy, C. Taylor-Rubin, B. Taylor, et al., "Symptom-Based Staging for Logopenic Variant Primary Progressive Aphasia," *European Journal of Neurology* 31 (2024): e16304.

7. S. Mazzeo, C. Polito, S. Padiglioni, et al., "Linguistic Profiles, Brain Metabolic Patterns and Rates of Amyloid-β Biomarker Positivity in Patients With Mixed Primary Progressive Aphasia," *Neurobiology of Aging* 96 (2020): 155–164.

8. G. Measso, F. Cavarzeran, G. Zappalà, et al., "The Mini-Mental State Examination: Normative Study of an Italian Random Sample," *Developmental Neuropsychology* 9 (1993): 77–85.

9. H. Spinnler and G. Tognoni, "Standardizzazione e Taratura Italiana di Una Batteria di Test Neuropsicologici," *Neurological Sciences* 6 (1987): S1–S120.

10. A. R. Giovagnoli, M. Del Pesce, S. Mascheroni, M. Simoncelli, M. Laiacona, and E. Capitani, "Trail Making Test: Normative Values From 287 Normal Adult Controls," *Neurological Sciences* 17 (1996): 305–309.

11. I. Appollonio, M. Leone, V. Isella, et al., "The Frontal Assessment Battery (FAB): Normative Values in an Italian Population Sample," *Neurological Sciences* 26 (2005): 108–116.

12. A. Basso, E. Capitani, and M. Laiacona, "Raven's Coloured Progressive Matrices: Normative Values on 305 Adult Normal Controls," *Functional Neurology* 2 (1987): 2189–2194.

13. G. Novelli, C. Papagno, E. Capitani, M. Laiacona, G. Vallar, and S. F. Cappa, "Tre Test Clinici di Ricerca e Produzione Lessicale. Taratura su Sogetti Normali," *Archivio di Psicologia, Neurologia e Psichiatria* 47 (1986): 477–506.

14. E. Kaplan, H. Goodglass, and S. Weintraub, *The Boston Naming Test* (Lea & Febiger, 1993).

15. G. Novelli, C. Papagno, E. Capitani, M. Laiacona, S. F. Cappa, and G. Vallar, "Tre Test Clinici di Memoria Verbale a Lungo Termine: Taratura su Soggetti Normali," *Archivio di Psicologia, Neurologia e Psichiatria* 47 (1986): 278–296.

16. A. Orsini, D. Grossi, E. Capitani, M. Laiacona, C. Papagno, and G. Vallar, "Verbal and Spatial Immediate Memory Span: Normative Data From 1355 Adults and 1112 Children," *Neurological Sciences* 8 (1987): 537–548.

17. M. Monaco, A. Costa, C. Caltagirone, and G. A. Carlesimo, "Forward and Backward Span for Verbal and Visuo-Spatial Data: Standardization and Normative Data From an Italian Adult Population," *Neurological Sciences* 34 (2013): 749–754.

18. S. Mondini, D. Mapelli, A. Vestri, and P. S. Bisiacchi, *Esame Neuropsicologico Breve* (Raffaello Cortina, 2003).

19. S. Katz, A. B. Ford, R. W. Moskowitz, B. A. Jackson, and M. W. Jaffe, "Studies of Illness in the Aged: The Index of ADL: A Standardized Measure of Biological and Psychosocial Function," *JAMA* 185 (1963): 914–919.

20. M. P. Lawton and E. M. Brody, "Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living," *Gerontologist* 9 (1969): 179–186.

21. B. R. Brooks, R. G. Miller, M. Swash, and T. L. Munsat, "El Escorial Revisited: Revised Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis," *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders* 1 (2000): 293–299.

22. E. N. Aiello, S. Feroldi, G. De Luca, et al., "Primary Progressive Aphasia and Motor Neuron Disease: A Review," *Frontiers in Aging Neuroscience* 14 (2022): 1003792.

23. S. A. Kremen, M. F. Mendez, P. H. Tsai, and E. Teng, "Extrapyramidal Signs in the Primary Progressive Aphasias," *American Journal of Alzheimer's Disease and Other Dementias* 26 (2011): 72–77.

24. J. M. Cedarbaum, N. Stambler, E. Malta, et al., "The ALSFRS-R: A Revised ALS Functional Rating Scale That Incorporates Assessments of Respiratory Function," *Journal of the Neurological Sciences* 169 (1999): 13–21.

25. C. G. Goetz, B. C. Tilley, S. R. Shaftman, et al., "Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results," *Movement Disorders* 23 (2008): 2129–2170.

26. E. Catricalà, E. Gobbi, P. Battista, et al., "SAND: A Screening for Aphasia in NeuroDegeneration. Development and Normative Data," *Neurological Sciences* 38 (2017): 1469–1483.

27. N. Patel, K. A. Peterson, R. U. Ingram, et al., "A 'Mini Linguistic State Examination'to Classify Primary Progressive Aphasia," *Brain Communications* 4 (2022): fcab299.

28. E. Canu, F. Agosta, G. Battistella, E. G. Spinelli, J. DeLeon, and M. L. Gorno-Tempini, "Speech Production Differences in English and Italian Speakers With Nonfluent Variant PPA," *Neurology* 94 (2020): e1062–e1072.

29. S. Mazzeo, C. J. Hardy, J. Jiang, et al., "Primary Progressive Aphasia in Italian and English: A Cross-Linguistic Cohort Study," *Neurology* 103 (2024): e210058.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Supporting information.