Title

Feasibility and safety of lumbar puncture in the Parkinson's disease research participants: Parkinson's Progression Marker Initiative (PPMI)

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Feasibility and safety of lumbar puncture in the Parkinson's disease research participants: Parkinson's Progression Marker Initiative (PPMI)

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Abstract

Objective: To determine the feasibility, safety and tolerability of lumbar punctures (LPs) in research participants with early Parkinson disease (PD), subjects without evidence of dopaminergic deficiency (SWEDDs) and healthy volunteers (HC).

Background: Cerebrospinal fluid (CSF) analysis is becoming an essential part of the biomarkers discovery effort in PD with still limited data on safety and feasibility of serial LPs in PD participants.

DESIGN/METHODS: Parkinson's Progression Marker Initiative (PPMI) is a longitudinal observation study designed to identify PD progression biomarkers. All PPMI participants undergo LP at baseline, 6, 12 months and yearly thereafter. CSF collection is performed by a trained investigator using predominantly atraumatic needles. Adverse events (AEs) are monitored by phone one week after LP completion. We analyzed safety data from baseline LPs.

Results: PPMI enrolled 683 participants (423 PD/196 HC/64 SWEDDs) from 23 study sites. CSF was collected at baseline in 97.5% of participants, of whom 5.4% underwent collection under fluoroscopy. 23% participants reported any related AEs, 68% of all AE were mild while 5.6% were severe. The most common AEs were headaches (13%) and low back pain (6.5%) and both occurred more commonly in HC and SWEDDs compared to PD participants. Factors associated with higher incidence of AEs across the cohorts included female gender, younger age and use of traumatic needles with larger diameter. AEs largely did not impact compliance with the future LPs.

Conclusions: LPs are safe and feasible in PD research participants. Specific LP techniques (needle type and gauge) may reduce the overall incidence of AEs.

Keywords

Parkinson's disease; Lumbar puncture; Safety; Adverse events

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.12.025.

1. Background

Collection of the cerebrospinal fluid (CSF) is becoming an essential part of the biomarkers development efforts in majority of neurodegenerative diseases. While there is a body of literature demonstrating feasibility of lumbar punctures (LPs) in Alzheimer's disease (AD) observational studies there still are limited data on repeated LPs in Parkinson's Disease (PD) population. PD patients notably have higher prevalence of spinal deformities like kyphpscoliosis that could influence the feasibility and safety of LP's [1,2].

The primary objectives of this analysis were to determine the safety and feasibility of completing LPs in a multicenter study and to report the incidence and type of LP related adverse events (AE) specifically as related to CSF collection methods and LP techniques.

2. Method

We analyzed data from the Parkinson's Progression Marker Initiative (PPMI), an ongoing observational, international, multicenter study aimed to identify the clinical, serological, genetic, CSF and imaging biomarkers of PD progression in a large cohort of participants with de novo PD (at baseline) compared to healthy controls (HC). The study design and objectives are available at www.ppmi-info.org/study-design. CSF collection is integral for this study. The study was approved by the institutional review board at each site, and participants provided written informed consent. Detailed inclusion and exclusion criteria have been previously published [3]. Conditions precluding LP like prohibitive lumbar spinal disease, hematologic conditions or, anticoagulant use, are exclusionary. This analysis focused on the safety and completion rate of the baseline LP procedure with the assumption that baseline procedure will be expected to have the highest complication rate. Longitudinal analyses were restricted to examining compliance with repeat LPs. Data were downloaded on March 27, 2017.

Among PD and HCs CSF samples were collected at baseline, 6 months and then annually up to 60 months. Subjects without evidence of dopaminergic deficiency (SWEDDs) were followed for 2 years. LP was performed by either the site investigator (SI) or another qualified clinician designated by the SI. Training videos and instructions were provided to make the procedure standardized and reduce the rate of AE. A L4-L5 space approach in seated position using atraumatic 24G Sprotte spinal needle was encouraged however not compulsory. Approximately 15–20 ml of CSF were required to be collected during each procedure. The protocol for LP procedure and CSF collection/processing are available in the PPMI Biologies manual (http://ppmi-info.org/).

Post LP instructions included lying horizontal for 30 min post procedure and avoiding exertional activities for 24-h. Standard preemptive instructions in case of mild to moderate headache included limiting physical activities, increasing oral fluids specifically caffeinated drinks, and trial of acetaminophen or ibuprofen as needed. In case of severe headaches, participants were asked to contact the site study staff.

Post procedure AEs were assessed by the site study staff during the time of visit and via phone 7–10 days following the LP. The relatedness of the AE to the procedure and

intensity of AEs as per standard guidelines were judged by the SI. Post LP headache (PLPH) and back pain (PLBP) were considered AEs of interest as the most common AEs reported post LPs. The categorization of post procedural headaches as PLPH was per the SI. All participants who completed the baseline visit were included in the analysis and only LP-related AEs were analyzed.

3. Statistical analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Demographic and PD characteristics are reported for all participants and by group. LP collection characteristics are also reported for all participants. Frequencies of LP-related AEs at baseline were reported by group, and relative risks compared percentages of participants who had each type of AE in PD vs. HC or PD vs. SWEDDs. Fisher's exact and t-tests were used to compare demographic and LP collection characteristics in participants with LP-related AE vs. no AE at baseline; these comparisons were done in all participants and separately by group. A Fisher s exact test was also used to test for association between the occurrence of LP-related AE at baseline and attempt of LP at the year 1 visit. Relative risk also compared the risk of baseline LP-related AEs in the first 10 LPs attempted vs. the risk of AEs in the remaining LPs adjusted for site. Finally, an ANOVA model was used to compare mean CSF volume collected in all participants according to AE severity at baseline.

4. Results

Between June 2010 and May 2013, PPMI recruited 683 participants (423 PD/196 HC/64 SWEDDs) from 23 study sites. PD and HC were matched by gender and age. Baseline demographics have been previously published and provided in the Supplementary Table 1s [3]. Baseline LP was attempted in 99.4% (679/683) of participants. 91.9% (628/683) participants (393 PD/178 HC/57 SWEDDs) had full CSF collection; 5.6%(n = 38) had partial and 1.9%(n = 13) had no CSF collection. For this analysis, all attempted LPs (99.4%) were included. LP was most commonly performed in the sitting position (61.3%) via the L3-L4 interspace (65.8%) using the 24G atraumatic Sprotte needle (69.4%) [Supplementary Table 2s.]. 5.4% participants underwent collection under fluoroscopy guidance. Syringe suction was the most commonly utilized CSF collection method (60.8%). Mean CSF volume collected was 16.3ml (Standard Deviation 3.8). 78% of CSF samples had hemoglobin level below 200ng/ml indicating low incidence of traumatic LPs.

Total of 180 AEs in 153 (22.5%) participants were reported at baseline across the cohorts. Table 1 provides summary of all LP related AEs presented by groups (PD/HC/SWEDDs). The percent of participants who experienced any AEs was 20.2/26.0/27.4 for PD/HC/SWEDDs respectively. 68.3% of all AE were reported to be mild, 26.1% moderate and 5.6% severe. There were no serious LP related AEs and complications like iatrogenic meningitis or arachnoiditis were not observed. Most common AEs were PLPH, noted in 13% among all participants; 11.6/14.3/19.4% in PD/HC/SWEDD groups respectively, and PLBP, noted in 6.5% among all participants; 5.2/7.7/11.3 in PD/HC/SWEDD groups respectively. Mean resolution time was 4.4(0–182) days for all AEs and 3.4(0–15) days for PLPH. Contrary

to expectation, large volume CSF collection was not associated with severity of AEs (p = 0.0301), rather CSF volume was higher in the mild AE group (mean = 17.1 ml) as compared to severe AE group (mean = 16.2 ml), moderate AE group (15 ml), and no AE group (16.2 ml).

Overall the relative risk of having PLPH in PD participants was lower compared to HCs (RR – 0.81, 95% CI – 0.53–1.25) and SWEDDs (RR – 0.60, 95% CI 0.34–1.06). Similarly, the relative risk of having PLBP was also lower in PD subgroup compared to HCs (RR 0.68, 95% CI 0.36–1.28) and SWEDDs (RR 0.46, 95% CI 0.21–1.03).

There was higher relative risk of having AEs in the first 10 baseline LPs compared to the remaining LP's when adjusted for the site (RR = 1.4% CI = 1.05–1.84). 76.4% of participants who had baseline LP related AEs and 87% of participants without LP related AEs went on to attempt the LP procedure at Year 1. At the end of 60 months, a total of 66% of expected participants completed the LP procedure.

4.1. Factors affecting the incidence of any LP related AE

We then explored what participant and procedure characteristics were associated with the LP related AE's (Table 2). AEs were higher among the females overall (F: 30.5%, M: 18.2%, p = 0.0004), driven by the HC (F: 38.6%, M: 19.1%, p = 0.004) and SWEDDs (F: 45.8%, M: 15.8%, p = 0.018) subgroup. Among all participants, those who had AE were younger (p = 0.004). This age difference was significant in HC (p = 0.04) but not in PD (p = 0.2) or SWEDDs (p = 0.08). Weight and CSF volume had no significant effect on the incidence of AE. Use of atraumatic Sprotte and high gauge Quincke needle were associated with lower incidence of AEs among all participants (p = 0.004). These results were driven by the PD subgroup (p = 0.006) as they were not significant in the HC and SWEDD subgroups. CSF collection method, LP site, and LP position had no significant bearing on the incidence of AEs among all participants and across the subgroups. CSF hemoglobin level which was considered a proxy for traumatic LP's, also did not have any impact on the AE's. Only age was associated with severity of the AEs (p = 0.0085), older participants had lower odds of developing moderate/severe as compared to mild AEs (OR- 0.955, CI: 0.923, 0.988).

4.2. Factors affecting the incidence of LP related headaches

PLPH were more common in the younger age group (mean age: 58.1 years, p = 0.001) and in participants with shorter height (mean height 170.1 cms, p = 0.01) overall. Association with age was driven by SWEDDs (p = 0.018) subgroup, while height was not significant in any subgroups. In the multivariate analysis, older age (OR 0.954, CI-0.930–0.978), male gender (OR - 0.477, CI- 0.283-0.805) and use of 24G Sprotte needle as compared to 18 G Quincke needle (OR 0.108, CI-0.021-0.563) had lower odds of PLPH. Sitting LP position had higher odds of PLPH when compared to lying down LP position (OR- 2.274, CI: 1.223–4.230). CSF collection method or LP site had no statistically significant effect on PLPH. Body mass Index (BMI), weight and volume of CSF collected had no significant effect on the incidence of PLPH when controlled for gender.

5. Discussion

To our knowledge, our analysis is the first to report data on LPs in a multicenter longitudinal study of PD participants. Our data support and build on the experience reported in the AD studies [4–7].The rate of any AEs in AD studies ranged from 11.3 to 36% with PLPH between 0.93 and 24% and PLBP from 4 to 17% [5–10]. Studies which exclusively used atraumatic Sprotte and Whitacre needles reported much lower AE with PLPH as low as 0.93% [7,9,11]. In our cohort, 23% of all participants and 20% of PD participants experienced any form of AE's well within the spectrum previously reported in AD population [4–7,9–11]. As expected PLPH and PLBP were the most common AEs interestingly with a lower rate in PD subgroup. Majority of AEs were mild (58%) with unexpectedly lower incidence of moderate to severe AE in older age group. The same was true for lower incidence of PLPH in older age group which is likely a contributor to lower rate of PLPH in our cohort in comparison to general population [5,6,10–12]. Females had a higher rate of AE consistent with previous studies and males had lower odds of developing PLPH [5,10]. The reason for gender effect is not clear as neither BMI nor height were significant. Volume of CSF did not have an impact on the incidence of AE's consistent with the previous studies [10]. This is reassuring considering that research studies might require a higher volume to reserve fluid for future analysis.

The lower rate of AEs could be attributed to increased utilization of atraumatic Sprotte needle and lying down LP position in our cohort. Sprotte needle is associated with reduced incidence and severity of AEs particularly PLPH [12,13]. Our analysis also demonstrates significantly lower incidence of AE with higher gauge traumatic needle, although this finding is not supported by the recent Cochrane review [12]. While the rate of PLPH was 13% in our cohort, it could have been potentially lower when compared to AD studies that exclusively used atraumatic needles [7,9,11].

While our analysis focused on baseline LP procedure highlighting high baseline LP rate of 99%, PPMI longitudinal data demonstrate fairly high percent LP retention rate over 5 years. The presence of AE's did not affect the subsequent LPs as 76% participants with AE at baseline attempted LP at year 1 and 66% of expected participants completed LP at 60 months. Our data reaffirm the feasibility of performing multiple LP's in cohorts of participants with PD with significant completion rate even at 60 months.

6. Conclusion

In summary, consistent with the data reported in the AD literature, our analysis shows that LP is overall safe and feasible in PD participants and can be routinely utilized in clinical trials and as a diagnostic test in the future if indicated. Based on our findings, apart from receiving formal training in performing LP, the clinicians and investigators planning to perform routine LPs are encouraged to use atraumatic Sprotte needles and lying down LP position to reduce the risk of AEs. Higher volume of CSF was not an obstacle for a safe procedure. Lastly, we also want to emphasize the importance of community education to increase acceptance of LPs as commonly utilized procedures in PD clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

LP-related adverse events at baseline by group.

Adverse Event	Group													
	PD Subjects				Healthy Controls				SWEDD Subjects				RR (95% CI)	
	(N = 421)				(N = 196)				(N = 62)					
	# of Subjects	% of Subjects	# of Events	Rate	# of Subjects	% of Subjects	# of Events	Rate	# of Subjects	% of Subjects	# of Events	Rate	PD vs. HC	PD vs. SWEDD
Total	85	20.2%	100	0.238	51	26.0%	59	0.301	17	27.4%	21	0.339	0.78 (0.58, 1.06)	0.74 (0.47, 1.16)
Most Common														
Post-LP Headache	49	11.6%	49	0.116	28	14.3%	28	0.143	12	19.4%	12	0.194	0.81 (0.53, 1.25)	0.60 (0.34, 1.06)
Post-LP Back Pain	22	5.2%	23	0.055	15	7.7%	15	0.077	7	11.3%	7	0.113	0.68 (0.36, 1.28)	0.46 (0.21, 1.03)
Ear														
Tinnitus	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Gastrointestinal														
Abdominal pain	0	0.0%	0	0.000	1	0.5%	1	0.005	0	0.0%	0	0.000	.	.
Nausea	4	1.0%	4	0.010	1	0.5%	1	0.005	0	0.0%	0	0.000	1.86 (0.21, 16.53)	.
Vomiting	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
General														
Fatigue	1	0.2%	1	0.002	1	0.5%	1	0.005	0	0.0%	0	0.000	0.47 (0.03, 7.48)	.
Pain	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Musculoskeletal														
Musculoskeletal pain	0	0.0%	0	0.000	1	0.5%	1	0.005	0	0.0%	0	0.000	.	.
Musculoskeletal stiffness	2	0.5%	2	0.005	1	0.5%	1	0.005	0	0.0%	0	0.000	0.93 (0.08, 10.20)	.

Adverse Event	Group													
	PD Subjects				Healthy Controls				SWEDD Subjects				RR (95% CI)	
	(N = 421)				(N = 196)				(N = 62)					
	# of Subjects	% of Subjects	# of Events	Rate	# of Subjects	% of Subjects	# of Events	Rate	# of Subjects	% of Subjects	# of Events	Rate	PD vs. HC	PD vs. SWEDD
Pain in extremity	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Post-LP Back Pain	22	5.2%	23	0.055	15	7.7%	15	0.077	7	11.3%	7	0.113	0.68 (0.36, 1.28)	0.46 (0.21, 1.03)
Post-LP Injection Site Pain	4	1.0%	4	0.010	1	0.5%	1	0.005	2	3.2%	2	0.032	1.86 (0.21, 16.53)	0.29 (0.05, 1.55)
Nervous System														
Dizziness	3	0.7%	3	0.007	2	1.0%	2	0.010	0	0.0%	0	0.000	0.70 (0.12, 4.16)	.
Intracranial hypotension	0	0.0%	0	0.000	1	0.5%	1	0.005	0	0.0%	0	0.000	.	.
Loss of consciousness	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Migraine	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Paraesthesia	0	0.0%	0	0.000	1	0.5%	1	0.005	0	0.0%	0	0.000	.	.
Parkinson's disease	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Post-LP Headache	49	11.6%	49	0.116	28	14.3%	28	0.143	12	19.4%	12	0.194	0.81 (0.53, 1.25)	0.60 (0.34, 1.06)
Presyncope	0	0.0%	0	0.000	1	0.5%	1	0.005	0	0.0%	0	0.000	.	.
Radicular pain	2	0.5%	2	0.005	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Syncope	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Procedural Related Injuries														
Contusion	1	0.2%	1	0.002	0	0.0%	0	0.000	0	0.0%	0	0.000	.	.
Post-LP Injection Site Pain	3	0.7%	3	0.007	5	2.6%	5	0.026	0	0.0%	0	0.000	0.28 (0.07, 1.16)	.

Column definitions.

# of Subjects: Number of subjects who had AE.

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% of Subjects: Percentage of subjects who had AE.

# of Events: Total number of AEs; includes multiple AEs of same type per subject.

Rate: Number of AEs per total number of subjects.

RR(95% CI): Relative Risk and 95% Confidence Interval for comparing percentages of subjects who had AE in PD subjects vs. healthy controls or PD subjects vs. SWEDD subjects.

Table 2

Incidence of all LP-Related AEs at baseline based on LP procedure characteristics.

Variable	All Subjects			PD Subjects			Healthy Controls			SWEDD Subjects		
	AE	No AE	p-value	AE	No AE	p-value	AE	No AE	p-value	AE	No AE	p-value
Age			0.1073			0.5752			0.1777			0.6316
< 56 years	52 (27.23%)	139 (72.77%)		27 (23.68%)	87 (76.32%)		18 (32.73%)	37 (67.27%)		7 (31.82%)	15 (68.18%)	
56–65 years	56 (22.67%)	191 (77.33%)		29 (19.08%)	123 (80.92%)		21 (27.63%)	55 (72.37%)		6 (31.58%)	13 (68.42%)	
> 65 years	45 (18.67%)	196 (81.33%)		29 (18.71%)	126 (81.29%)		12 (18.46%)	53 (81.54%)		4 (19.05%)	17 (80.95%)	
Gender			0.0004			0.1603			0.0038			0.0180
Male	80 (18.18%)	360 (81.82%)		50 (18.12%)	226 (81.88%)		24 (19.05%)	102 (80.95%)		6 (15.79%)	32 (84.21%)	
Female	73 (30.54%)	166 (69.46%)		35 (24.14%)	110 (75.86%)		27 (38.57%)	43 (61.43%)		11 (45.83%)	13 (54.17%)	
Type of Needle			0.0039			0.0060			0.0782			0.3473
20g Quincke	19 (38.78%)	30 (61.22%)		14 (42.42%)	19 (57.58%)		3 (27.27%)	8 (72.73%)		2 (40.00%)	3 (60.00%)	
22g Quincke	20 (30.30%)	46 (69.70%)		12 (27.27%)	32 (72.73%)		6 (42.86%)	8 (57.14%)		2 (25.00%)	6 (75.00%)	
25g Quincke	1 (7.69%)	12 (92.31%)		0 (0.00%)	8 (100.0%)		1 (50.00%)	1 (50.00%)		0 (0.00%)	3 (100.0%)	
22g Sprotte	12 (18.75%)	52 (81.25%)		4 (10.26%)	35 (89.74%)		6 (28.57%)	15 (71.43%)		2 (50.00%)	2 (50.00%)	
24g Sprotte	92 (19.53%)	379 (80.47%)		51 (17.71%)	237 (82.29%)		32 (22.22%)	112 (77.78%)		9 (23.08%)	30 (76.92%)	
18g	4 (50.00%)	4 (50.00%)		1 (20.00%)	4 (80.00%)		2 (100.0%)	0 (0.00%)		1 (100.0%)	0 (0.00%)	
Unknown/Missing	5 (62.50%)	3 (37.50%)		3 (75.00%)	1 (25.00%)		1 (50.00%)	1 (50.00%)		1 (50.00%)	1 (50.00%)	
Method of Collection			0.0857			0.3769			0.1713			0.5676
Gravity	66 (25.58%)	192 (74.42%)		36 (22.09%)	127 (77.91%)		22 (31.88%)	47 (68.12%)		8 (30.77%)	18 (69.23%)	
Syringe Suction	82 (19.85%)	331 (80.15%)		46 (18.11%)	208 (81.89%)		28 (22.40%)	97 (77.60%)		8 (23.53%)	26 (76.47%)	
Unknown/Missing	5 (62.50%)	3 (37.50%)		3 (75.00%)	1 (25.00%)		1 (50.00%)	1 (50.00%)		1 (50.00%)	1 (50.00%)	
Lumbar Puncture Site			0.2801			0.3671			0.3285			0.7516
L2-L3 Interspace	7 (20.59%)	27 (79.41%)		4 (17.39%)	19 (82.61%)		1 (14.29%)	6 (85.71%)		2 (50.00%)	2 (50.00%)	
L3-L4 Interspace	93 (20.81%)	354 (79.19%)		47 (17.87%)	216 (82.13%)		34 (23.94%)	108 (76.06%)		12 (28.57%)	30 (71.43%)	
L4-L5 Interspace	41 (26.97%)	111 (73.03%)		25 (24.27%)	78 (75.73%)		14 (35.00%)	26 (65.00%)		2 (22.22%)	7 (77.78%)	
Unknown/Missing	12 (26.09%)	34 (73.91%)		9 (28.13%)	23 (71.88%)		2 (28.57%)	5 (71.43%)		1 (14.29%)	6 (85.71%)	
Subject position during LP			0.0737			0.5083			0.1688			0.3495
Sitting, leaned over	98 (23.56%)	318 (76.44%)		50 (19.84%)	202 (80.16%)		37 (29.60%)	88 (70.40%)		11 (28.21%)	28 (71.79%)	

Variable	All Subjects			PD Subjects			Healthy Controls			SWEDD Subjects		
	AE	No AE	p-value	AE	No AE	p-value	AE	No AE	p-value	AE	No AE	p-value
Lying, curled up on side	41 (17.52%)	193 (82.48%)		25 (16.67%)	125 (83.33%)		13 (20.00%)	52 (80.00%)		3 (15.79%)	16 (84.21%)	
Unknown/Missing	14 (48.28%)	15 (51.72%)		10 (52.63%)	9 (47.37%)		1 (16.67%)	5 (83.33%)		3 (75.00%)	1 (25.00%)	
CSF Hemoglobin			0.4815			0.8795			0.2845			0.4681
< 200 ng/ml	115 (21.70%)	415 (78.30%)		66 (20.12%)	262 (79.88%)		37 (24.03%)	117 (75.97%)		12 (25.00%)	36 (75.00%)	
200 ng/ml or above	32 (24.62%)	98 (75.38%)		16 (19.05%)	68 (80.95%)		12 (34.29%)	23 (65.71%)		4 (36.36%)	7 (63.64%)	
Missing	6 (31.58%)	13 (68.42%)		3 (33.33%)	6 (66.67%)		2 (28.57%)	5 (71.43%)		1 (33.33%)	2 (66.67%)	

Note: p-values come from Fisher’s Exact Tests.